

EXHIBIT A

EXHIBIT A—AGREED-UPON CONSTRUCTIONS

Claim Term	Corresponding Claims	Agreed-Upon Construction
“about”	’868 patent, claims 1, 8-14, 21-26, 28; ’482 patent, claims 1, 7-14, 20-28; ’621 patent, claims 1, 5-8, 13-19, 21-24, 27-30; and incorporated in all dependent claims thereto	“approximately”

EXHIBIT B

EXHIBIT B—DISPUTED CONSTRUCTIONS BETWEEN SILVERGATE AND DEFENDANTS

Claim Term	Corresponding Claims	Silvergate’s Proposed Construction and Evidence	Defendant’s Proposed Construction and Evidence
“consisting essentially of”	<p>’868 patent, claims 1, 13, 14, 26, and incorporated in all dependent claims thereto;</p> <p>’621 patent claims 1-30¹</p>	<p><u>PROPOSED CONSTRUCTION:</u></p> <p>Plain and ordinary meaning (not indefinite)</p> <p><u>EXEMPLARY INTRINSIC EVIDENCE:</u></p> <p>Silvergate reserves the right to rely on the claims, specifications, and entire prosecution histories of the ’868, ’482, and ’621 patents, as well as those of U.S. Patent No. 9,669,008 (“’008 patent”), 9,808,442 (“’442 patent”), 10,039,745 (“’745 patent”), and 10,154,987 (“’987 patent”), and all related patent applications, including but not limited to:</p> <p><u>’868 Patent</u></p> <ul style="list-style-type: none"> - Claims 1-30 <p><u>’868 Patent</u></p> <ul style="list-style-type: none"> - Abstract - col. 1:49-52 - col. 2:21-28 - col. 4:64-5:8 - col. 5:13-23 	<p><u>PROPOSED CONSTRUCTION:</u></p> <p>This term is indefinite</p> <p><u>INTRINSIC EVIDENCE:</u></p> <p><u>’868 patent</u></p> <p>Claim 1–30; 2:21–3:49; 4:64–5:9; 5:54–6:55; 8:35–19:54; 20:43–22:44; 23:19–67; 31:19–41:27 (Examples A–H).</p> <p><u>Prosecution history of U.S. Patent No. 9,669,008</u></p> <p>Original Claims (SLVGT-EPA_0000365–366); Office Action dated January 17, 2017 (SLVGT-EPA_0000835–841); February 3, 2017 Amendment and Response (SLVGT-EPA_0000857-879); Mosher Declaration dated February 2, 2017 at 1-8 (SLVGT-EPA_0000880-87);</p>

¹ Bionpharma did not identify this term with respect to the ’621 patent in its disclosure of claim terms and proposed constructions on March 17, 2021.

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Defendant's Proposed Construction and Evidence
		<ul style="list-style-type: none"> - col. 5:45-50 - col. 5:58-6:15 - col. 6:22-55 - col. 10:23-60 - col. 13:22-14:25 - col. 14:47-48 - col. 18:36-19:35 - col. 25:27-61 - col. 29:16-18 - Examples A-H and all associated tables - Figs. 1 & 2 <p><u>File History of '008 Patent</u></p> <ul style="list-style-type: none"> - Jan. 17, 2017 – First Action Interview (SLVGT-EPA_0000835-837) - Feb. 3, 2017 – Response to Non-Final Office Action (SLVGT-EPA_0000857-879) - Feb. 3, 2017 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0000880-893) - Mar. 22, 2017 – Supplemental Amendment in Response to Non-Final Office Action (SLVGT-EPA_0000940-945) - Apr. 19, 2017 – Notice of Allowance (SLVGT-EPA_0001145-149) <p><u>File History of '868 Patent</u></p> <ul style="list-style-type: none"> - Jan. 8, 2019 – Preliminary Amendment (SLVGT-EPA_0104422-428) 	<p>Supplemental Amendment dated March 22, 2017 (SLVGT-EPA_0000940–945); Notice of Allowance dated April 19, 2017 (SLVGT-EPA_0001145–151).</p> <p><u>'868 Patent Prosecution history</u> Original claims at 48-51; Preliminary amendment dated January 18, 2019; Office Action dated May 2, 2019; August 1, 2019 Office Action Response; Declarations of Mosher dated February 2, 2017 and May 14, 2020; Office Action dated Nov 19, 2019; May 14, 2020 Office Action Response; Notice of Allowance dated August 8, 2020.</p> <p><u>'482 Patent Prosecution history</u> Original claims at 48-51; Office Action dated January 25, 2019; March 1, 2019 Office Action Response; Declarations of Mosher dated February 2, 2017 and May 14, 2020; Office Action dated June 24, 2019; August 1, 2019 Office Action Response; Advisory Opinion dated September 16, 2019; October 24, 2019 Office Action Response; Office Action dated January 7, 2020; May 15, 2020 Office Action Response; Notice of allowance dated July 16, 2020.</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Defendant's Proposed Construction and Evidence
		<ul style="list-style-type: none"> - Aug. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105316-330) - Aug. 1, 2020 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105341-354) - May 14, 2017 – Declaration of Dr. Mosher dated May 14, 2020 (SLVGT-EPA_0105503-513) - May 14, 2020 – Response of Final Office Action (SLVGT-EPA_0105519-532) - Aug. 3, 2020 – Notice of Allowance (SLVGT-EPA_0105656-663) <p><u>File History of '482 Patent</u></p> <ul style="list-style-type: none"> - Mar. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105790-803) - Mar. 1, 2019 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105804-817) - Aug. 1, 2019 – Response to Final Office Action (SLVGT-EPA_0106721-728) - Oct. 24, 2019 – Response to Advisory Action and Final Office Action (SLVGT-EPA_0106753-760) - May 15, 2020 – Response to Non-Final Office Action (SLVGT-EPA_0106791-801) - May 15, 2020 – Declaration of Dr. Mosher dated May 15, 2020 (SLVGT-EPA_0106802-808) 	

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Defendant's Proposed Construction and Evidence
		- July 16, 2020 – Notice of Allowance (SLVGT-EPA_0106991-6999)	
“wherein the formulation is stable at about 5±3°C for at least 12 months”	'868 patent, claims 1, 13, 14, 26, and incorporated in all dependent claims thereto	<p><u>PROPOSED CONSTRUCTION:</u></p> <p>Plain and ordinary meaning (not indefinite)</p> <p><u>EXEMPLARY INTRINSIC EVIDENCE:</u></p> <p>Silvergate reserves the right to rely on the claims, specifications, and entire prosecution histories of the '868, '482, and '621 patents, as well as the '008, '442, '745, and '987 patents, and all related patent applications, including but not limited to:</p> <p><u>'868 Patent</u></p> <ul style="list-style-type: none"> - Claims 1-30 <p><u>'868 Patent</u></p> <ul style="list-style-type: none"> - Abstract - col. 1:49-52 - col. 2:21-28 - col. 4:64-5:8 - col. 5:13-23 - col. 5:45-50 - col. 5:58-6:15 	<p><u>PROPOSED CONSTRUCTION:</u></p> <p>This term is indefinite (to the extent it is not unbounded and thus invalid for lack of written description and/or enablement)²</p> <p><u>INTRINSIC EVIDENCE:</u></p> <p><u>'868 patent</u></p> <p>Claim 1–30; 2:21–3:49; 4:64–5:9; 5:54–6:55; 8:35–19:54; 20:43–22:44; 23:19–67; 31:19–41:27 (Examples A–H).</p> <p><u>'482 patent</u></p> <p>Claim 1-28; 2:21–3:49; 4:64–5:9; 5:54–6:55; 8:35–19:54; 20:43–22:44;</p>

² This position is made without prejudice to Amneal's arguments in C.A. No. 19-678 that the same or similar claim limitations in the patents asserted in that case are invalid for lack of written description and/or enablement.

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Defendant's Proposed Construction and Evidence
		<ul style="list-style-type: none"> - col. 13:22-14:25 - col. 14:47-48 - col. 18:36-19:35 - col. 25:27-61 - col. 29:16-18 - Examples A-H and all associated tables - Figs. 1 & 2 <p><u>File History of '008 Patent</u></p> <ul style="list-style-type: none"> - Jan. 17, 2017 – First Action Interview (SLVGT-EPA_0000835-837) - Feb. 3, 2017 – Response to Non-Final Office Action (SLVGT-EPA_0000857-879) - Feb. 3, 2017 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0000880-893) - Mar. 22, 2017 – Supplemental Amendment in Response to Non-Final Office Action (SLVGT-EPA_0000940-945) - Apr. 19, 2017 – Notice of Allowance (SLVGT-EPA_0001145-149) <p><u>File History of '868 Patent</u></p> <ul style="list-style-type: none"> - Jan. 8, 2019 – Preliminary Amendment (SLVGT-EPA_0104422-428) - Aug. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105316-330) - Aug. 1, 2020 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105341-354)May 14, 2017 – Declaration of Dr. 	<p>23:19–67; 31:14–41:10 (Examples A–H).</p> <p><u>Prosecution history of U.S. Patent No. 9,669,008</u> Original Claims (SLVGT-EPA_0000365–366); Office Action dated January 17, 2017 (SLVGT-EPA_0000835–841); February 3, 2017 Amendment and Response (SLVGT-EPA_0000857-879); Mosher Declaration dated February 2, 2017 at 1-8 (SLVGT-EPA_0000880-87); Supplemental Amendment dated March 22, 2017 (SLVGT-EPA_0000940–945); Notice of Allowance dated April 19, 2017 (SLVGT-EPA_0001145–151).</p> <p><u>'868 Patent Prosecution history</u> Original claims at 48-51; Preliminary amendment dated January 18, 2019; Office Action dated May 2, 2019; August 1, 2019 Office Action Response; Declarations of Mosher dated February 2, 2017 and May 14, 2020; Office Action dated Nov 19, 2019; May 14, 2020 Office Action Response; Notice of Allowance dated August 8, 2020.</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Defendant's Proposed Construction and Evidence
		<p>Mosher dated May 14, 2020 (SLVGT-EPA_0105503-513)</p> <ul style="list-style-type: none"> - May 14, 2020 – Response of Final Office Action (SLVGT-EPA_0105519-532) - Aug. 3, 2020 – Notice of Allowance (SLVGT-EPA_0105656-663) <p><u>File History of '482 Patent</u></p> <ul style="list-style-type: none"> - Mar. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105790-803) - Mar. 1, 2019 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105804-817) - Aug. 1, 2019 – Response to Final Office Action (SLVGT-EPA_0106721-728) - Oct. 24, 2019 – Response to Advisory Action and Final Office Action (SLVGT-EPA_0106753-760) - May 15, 2020 – Response to Non-Final Office Action (SLVGT-EPA_0106791-801) - May 15, 2020 – Declaration of Dr. Mosher dated May 15, 2020 (SLVGT-EPA_0106802-808) - July 16, 2020 – Notice of Allowance (SLVGT-EPA_0106991-6999) 	<p><u>'482 Patent Prosecution history</u></p> <p>Original claims at 48-51; Office Action dated January 25, 2019; March 1, 2019 Office Action Response; Declarations of Mosher dated February 2, 2017 and May 14, 2020; Office Action dated June 24, 2019; August 1, 2019 Office Action Response; Advisory Opinion dated September 16, 2019; October 24, 2019 Office Action Response; Office Action dated January 7, 2020; May 15, 2020 Office Action Response; Notice of allowance dated July 16, 2020.</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Defendant's Proposed Construction and Evidence
"wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about 5±3°C"	'482 patent claims 1, 13, 14, and incorporated in all dependent claims thereto	<p><u>PROPOSED CONSTRUCTION:</u></p> <p>Plain and ordinary meaning (not indefinite)</p> <p><u>EXEMPLARY INTRINSIC EVIDENCE:</u></p> <p>Silvergate reserves the right to rely on the claims, specifications, and entire prosecution histories of the '868, '482, and '621 patents, as well as the '008, '442, '745, and '987 patents, and all related patent applications, including but not limited to:</p> <p><u>'482 Patent</u></p> <ul style="list-style-type: none"> - Claims 1-28 <p><u>'868 Patent³</u></p> <ul style="list-style-type: none"> - Abstract - col. 1:49-52 - col. 2:21-28 - col. 4:64-5:8 - col. 5:13-23 - col. 5:45-50 - col. 5:58-6:15 	<p><u>PROPOSED CONSTRUCTION:</u></p> <p>This term is indefinite (to the extent it is not unbounded and thus invalid for lack of written description and/or enablement)⁴</p> <p><u>INTRINSIC EVIDENCE:</u></p> <p><u>'868 patent</u> Claim 1–30; 2:21–3:49; 4:64–5:9; 5:54–6:55; 8:35–19:54; 20:43–22:44; 23:19–67; 31:19–41:27 (Examples A–H).</p> <p><u>'482 patent</u> Claim 1-28; 2:21–3:49; 4:64–5:9; 5:54–6:55; 8:35–19:54; 20:43–22:44;</p>

³ The 868, '482, and '621 patents and the '008, '442, '745, and '987 patents all share the same specification. References to any of the patents in this group includes all citations to equivalent portions of other patents in the group.

⁴ This position is made without prejudice to Amneal's arguments in C.A. No. 19-678 that the same or similar claim limitations in the patents asserted in that case are invalid for lack of written description and/or enablement.

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Defendant's Proposed Construction and Evidence
		<ul style="list-style-type: none"> - col. 13:22-14:25 - col. 14:47-48 - col. 18:36-19:35 - col. 25:27-61 - col. 29:16-18 - Examples A-H and all associated tables - Figs. 1 & 2 <p><u>File History of '008 Patent</u></p> <ul style="list-style-type: none"> - Jan. 17, 2017 – First Action Interview (SLVGT-EPA_0000835-837) - Feb. 3, 2017 – Response to Non-Final Office Action (SLVGT-EPA_0000857-879) - Feb. 3, 2017 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0000880-893) - Mar. 22, 2017 – Supplemental Amendment in Response to Non-Final Office Action (SLVGT-EPA_0000940-945) - Apr. 19, 2017 – Notice of Allowance (SLVGT-EPA_0001145-149) <p><u>File History of '868 Patent</u></p> <ul style="list-style-type: none"> - Jan. 8, 2019 – Preliminary Amendment (SLVGT-EPA_0104422-428) - Aug. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105316-330) 	<p>23:19–67; 31:14–41:10 (Examples A–H).</p> <p><u>Prosecution history of U.S. Patent No. 9,669,008</u> Original Claims (SLVGT-EPA_0000365–366); Office Action dated January 17, 2017 (SLVGT-EPA_0000835–841); February 3, 2017 Amendment and Response (SLVGT-EPA_0000857-879); Mosher Declaration dated February 2, 2017 at 1-8 (SLVGT-EPA_0000880-87); Supplemental Amendment dated March 22, 2017 (SLVGT-EPA_0000940–945); Notice of Allowance dated April 19, 2017 (SLVGT-EPA_0001145–151).</p> <p><u>'868 Patent Prosecution history</u> Original claims at 48-51; Preliminary amendment dated January 18, 2019; Office Action dated May 2, 2019; August 1, 2019 Office Action Response; Declarations of Mosher dated February 2, 2017 and May 14, 2020; Office Action dated Nov 19, 2019; May 14, 2020 Office Action Response; Notice of Allowance dated August 8, 2020.</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Defendant's Proposed Construction and Evidence
		<ul style="list-style-type: none"> - Aug. 1, 2020 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105341-354) - May 14, 2017 – Declaration of Dr. Mosher dated May 14, 2020 (SLVGT-EPA_0105503-513) - May 14, 2020 – Response of Final Office Action (SLVGT-EPA_0105519-532) - Aug. 3, 2020 – Notice of Allowance (SLVGT-EPA_0105656-663) <p><u>File History of '482 Patent</u></p> <ul style="list-style-type: none"> - Mar. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105790-803) - Mar. 1, 2019 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105804-817) - Aug. 1, 2019 – Response to Final Office Action (SLVGT-EPA_0106721-728) - Oct. 24, 2019 – Response to Advisory Action and Final Office Action (SLVGT-EPA_0106753-760) - May 15, 2020 – Response to Non-Final Office Action (SLVGT-EPA_0106791-801) - May 15, 2020 – Declaration of Dr. Mosher dated May 15, 2020 (SLVGT-EPA_0106802-808) - July 16, 2020 – Notice of Allowance (SLVGT-EPA_0106991-6999) 	<p><u>'482 Patent Prosecution history</u></p> <p>Original claims at 48-51; Office Action dated January 25, 2019; March 1, 2019 Office Action Response; Declarations of Mosher dated February 2, 2017 and May 14, 2020; Office Action dated June 24, 2019; August 1, 2019 Office Action Response; Advisory Opinion dated September 16, 2019; October 24, 2019 Office Action Response; Office Action dated January 7, 2020; May 15, 2020 Office Action Response; Notice of allowance dated July 16, 2020.</p>

EXHIBIT B—DISPUTED CONSTRUCTIONS SPECIFIC BETWEEN SILVERGATE AND BIONPHARMA

Claim Term	Corresponding Claims	Silvergate’s Proposed Construction and Evidence	Bionpharma’s Proposed Construction and Evidence
“buffer” ⁵	<p>’868 patent claims 1, 5, 6, 8-10, 13, 14, 18, 19, 21-23, 26, 30, and incorporated in all dependent claims thereto;</p> <p>’482 patent claims 1, 7, 8, 13, 14, 25, 26, 28, and incorporated in all dependent claims thereto;</p> <p>’621 patent claims 1, 4-7, 19, 20-23, 30, and incorporated in all dependent claims thereto</p>	<p><u>PROPOSED CONSTRUCTION:</u></p> <p>“agent(s) that adjust and/or maintain pH”</p> <p><u>EXEMPLARY INTRINSIC EVIDENCE:</u></p> <p>Silvergate reserves the right to rely on the claims, specifications, and entire prosecution histories of the ’868, ’482, and ’621 patents, as well as the ’008, ’442, ’745, and ’987 patents, and all related patent applications, including but not limited to:</p> <ul style="list-style-type: none"> - Claims of the ’868, ’482, and ’621 patents <p><u>’868 Patent</u></p> <ul style="list-style-type: none"> - Abstract - col. 1:49-52 - col. 2:21-28 - col. 4:64-5:8 - col. 5:13-23 - col. 5:45-50 - col. 5:58-6:15 - col. 6:29-31 - col. 6:35-40 	<p><u>PROPOSED CONSTRUCTIONS:</u></p> <p>(i) “a buffering agent or mixture of agents that maintain(s) the pH of the liquid enalapril formulation beyond any pH maintenance provided by enalapril, an enalapril salt, or any compound disassociated from an enalapril salt”</p> <p><i>or, alternatively</i></p> <p>(ii) “a buffering agent or mixture of agents that that includes a weak acid that has an acidic hydrogen with a pKa within ± 1 of the formulation pH”</p> <p><u>INTRINSIC EVIDENCE:</u></p> <p>’482 Patent 1:1-42:63</p> <p>’868 Patent 1:1-42:67</p> <p>’621 Patent 1:1-42:67</p> <p><u>’482 Patent File History:</u></p>

⁵ Amneal reserves the right to join Bionpharma’s proposed construction of the term “buffer.”

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Bionpharma's Proposed Construction and Evidence
		<ul style="list-style-type: none"> - col. 13:22-14:48 - col. 18:36-19:35 - col. 21:9-33 - col. 25:27-61 - col. 29:16-18 - col. 29:23-28 - Examples A-H and all associated tables - Figs. 1 & 2 <p><u>File History of '008 Patent</u></p> <ul style="list-style-type: none"> - Jan. 17, 2017 – First Action Interview (SLVGT-EPA_0000835-837) - Feb. 3, 2017 – Response to Non-Final Office Action (SLVGT-EPA_0000857-879) - Feb. 3, 2017 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0000880-893) - Mar. 22, 2017 – Supplemental Amendment in Response to Non-Final Office Action (SLVGT-EPA_0000940-945) - Apr. 19, 2017 – Notice of Allowance (SLVGT-EPA_0001145-149) <p><u>File History of '868 Patent</u></p> <ul style="list-style-type: none"> - Jan. 8, 2019 – Preliminary Amendment (SLVGT-EPA_0104422-428) - Aug. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105316-330) 	<p>2018-10-31 Claims - SLVGT-EPA_0105692-695</p> <p>2018-10-31 Specification - SLVGT-EPA_0105715-762</p> <p>2019-01-25 Non-Final Rejection - SLVGT-EPA_0105771-784</p> <p>2019-03-01 Response to Office Action - SLVGT-EPA_0105790-803</p> <p>2019-03-01 Mosher Declaration dated Feb 2, 2017 - SLVGT-EPA_0105804-811</p> <p>2019-06-24 Final Rejection - SLVGT-EPA_0106673-692</p> <p>2019-08-01 Response After Final - SLVGT-EPA_0106721-728</p> <p>2019-09-16 Advisory Opinion - SLVGT-EPA_0106743-745</p> <p>2019-08-22 Examiner Interview - SLVGT-EPA_0106746</p> <p>2019-10-24 Response to Office Action - SLVGT-EPA_0106753-760</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Bionpharma's Proposed Construction and Evidence
		<ul style="list-style-type: none"> - Aug. 1, 2020 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105341-354) - May 14, 2017 – Declaration of Dr. Mosher dated May 14, 2020 (SLVGT-EPA_0105503-513) - May 14, 2020 – Response of Final Office Action (SLVGT-EPA_0105519-532) - Aug. 3, 2020 – Notice of Allowance (SLVGT-EPA_0105656-663) <p><u>File History of '482 Patent</u></p> <ul style="list-style-type: none"> - Mar. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105790-803) - Mar. 1, 2019 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105804-817) - Aug. 1, 2019 – Response to Final Office Action (SLVGT-EPA_0106721-728) - Oct. 24, 2019 – Response to Advisory Action and Final Office Action (SLVGT-EPA_0106753-760) - May 15, 2020 – Response to Non-Final Office Action (SLVGT-EPA_0106791-801) - May 15, 2020 – Declaration of Dr. Mosher dated May 15, 2020 (SLVGT-EPA_0106802-808) - July 16, 2020 – Notice of Allowance (SLVGT-EPA_0106991-6999) 	<p>2020-01-07 Non-Final Rejection - SLVGT-EPA_0106767-777</p> <p>2020-03-06 Examiner Interview - SLVGT-EPA_0106788-790</p> <p>2020-05-15 Response to Office Action - SLVGT-EPA_0106791-801</p> <p>2020-05-15 Mosher Declaration dated May 15, 2020 - SLVGT-EPA_0106802-808</p> <p>2020-07-16 Notice of Allowance - SLVGT-EPA_0106991-999</p> <p>2020-07-01 Examiner Interview - SLVGT-EPA_0107000-001</p> <p>2020-07-22 Amendment after Notice of Allowance - SLVGT-EPA_0107030-036</p> <p>2020-07-31 Response to Amendment - SLVGT-EPA_0107044-045</p> <p>2020-08-22 Notice of Allowance - SLVGT-EPA_0107047-050</p> <p>2020-29-09 Issue Notification - SLVGT-EPA_0107056</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Bionpharma's Proposed Construction and Evidence
		<u>File History of '621 Patent</u> - Jan. 1, 2021 – Notice of Allowance (SLVGT-EPA_0107216-220)	<u>'868 Patent File History:</u> 2019-01-08 Claims - SLVGT-EPA_0104348-351 2019-01-08 Specification - SLVGT-EPA_0104374-421 2019-01-18 Preliminary Amendment - SLVGT-EPA_0104422-428 2019-05-02 Non-Final Rejection - SLVGT-EPA_0105281-296 2019-08-01 Response to Office Action - SLVGT-EPA_0105316-330 2019-08-01 Mosher Declaration dated Feb 2, 2017 - SLVGT-EPA_0105341-348 2019-11-19 Final Rejection - SLVGT-EPA_0105478-494 2020-05-14 Mosher Declaration dated May 14, 2020 - SLVGT-EPA_0105503-513 2020-05-14 Response to Office Action - SLVGT-EPA_0105519-532

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Bionpharma's Proposed Construction and Evidence
			<p>2020-07-22 Examiner Interview - SLVGT-EPA_0105664-665</p> <p>2020-08-03 Notice of Allowance - SLVGT-EPA_0105656-663</p> <p>2020-08-03 Examiner Interview - SLVGT-EPA_0105676</p> <p>2020-09-15 Issue Notification - SLVGT-EPA_0105686</p> <p><u>'621 Patent File History:</u></p> <p>2020-08-12 Specification – SLVGT-EPA_0107082-129</p> <p>2020-08-12 Claims – SLVGT-EPA_0107130-132</p> <p>2020-12-28 Mosher Declaration dated May 15, 2020 – SLVGT-EPA_0107181-187</p> <p>2020-12-28 Mosher Declaration dated May 14, 2020 – SLVGT-EPA_0107188-198</p> <p>2020-12-28 Mosher Declaration dated Feb 2, 2017 – SLVGT-EPA_0107199-206</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Bionpharma's Proposed Construction and Evidence
			<p>2020-12-28 Supplemental Response or Supplemental Amendment – SLVGT-EPA_0107209-211</p> <p>2021-01-01 Notice of Allowance – SLVGT-EPA_0107212-220</p> <p>2020-12-17 Examiner Interview – SLVGT-EPA_0107221-222</p> <p>2021-02-16 Issue Notification – SLVGT-EPA_0107260</p>
“wherein the formulation is stable at about 5±3°C for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity	'621 patent claims 1, 19, 30, and incorporated in all dependent claims thereto	<p><u>PROPOSED CONSTRUCTION:</u></p> <p>Plain and ordinary meaning (not indefinite)</p> <p><u>EXEMPLARY INTRINSIC EVIDENCE:</u></p> <p>Silvergate reserves the right to rely on the claims, specifications, and entire prosecution histories of the '868, '482, and '621 patents, as well as the '008, '442, '745, and '987 patents, and all related patent applications, including but not limited to:</p> <p><u>'621 Patent</u></p> <ul style="list-style-type: none"> - Claims 1-30 <p><u>'868 Patent</u></p> <ul style="list-style-type: none"> - Abstract 	<p><u>PROPOSED CONSTRUCTION:</u></p> <p>Indefinite (to the extent it is not unbounded and thus invalid for lack of written description and/or enablement)</p> <p><u>INTRINSIC EVIDENCE:</u></p> <p>This term is indefinite (to the extent it is not unbounded and thus invalid for lack of written description and/or enablement)</p> <p><u>'621 Patent</u> Claim 1-30</p> <p><u>'868 patent</u> Claim 1–30; 2:21–3:49; 4:64–5:9;</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Bionpharma's Proposed Construction and Evidence
or related substances at the end of a given storage period"		<ul style="list-style-type: none"> - col. 1:49-52 - col. 2:21-28 - col. 4:64-5:8 - col. 5:13-23 - col. 5:45-50 - col. 5:58-6:15 - col. 13:22-14:25 - col. 14:47-48 - col. 18:36-19:35 - col. 25:27-61 - col. 29:16-18 - Examples A-H and all associated tables - Figs. 1 & 2 <p><u>File History of '008 Patent</u></p> <ul style="list-style-type: none"> - Jan. 17, 2017 – First Action Interview (SLVGT-EPA_0000835-837) - Feb. 3, 2017 – Response to Non-Final Office Action (SLVGT-EPA_0000857-879) - Feb. 3, 2017 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0000880-893) - Mar. 22, 2017 – Supplemental Amendment in Response to Non-Final Office Action (SLVGT-EPA_0000940-945) - Apr. 19, 2017 – Notice of Allowance (SLVGT-EPA_0001145-149) 	<p>5:54–6:55; 8:35–19:54; 20:43–22:44; 23:19–67; 31:19–41:27 (Examples A–H).</p> <p><u>'482 patent</u> Claim 1-28; 2:21–3:49; 4:64–5:9; 5:54–6:55; 8:35–19:54; 20:43–22:44; 23:19–67; 31:14–41:10 (Examples A–H).</p> <p><u>Prosecution history of U.S. Patent No. 9,669,008</u> Original Claims (SLVGT-EPA_0000365–366); Office Action dated January 17, 2017 (SLVGT-EPA_0000835–841); February 3, 2017 Amendment and Response (SLVGT-EPA_0000857-879); Mosher Declaration dated February 2, 2017 at 1-8 (SLVGT-EPA_0000880-87); Supplemental Amendment dated March 22, 2017 (SLVGT-EPA_0000940–945); Notice of Allowance dated April 19, 2017 (SLVGT-EPA_0001145–151).</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Bionpharma's Proposed Construction and Evidence
		<p><u>File History of '868 Patent</u></p> <ul style="list-style-type: none"> - Jan. 8, 2019 – Preliminary Amendment (SLVGT-EPA_0104422-428) - Aug. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105316-330) - Aug. 1, 2020 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105341-354) - May 14, 2017 – Declaration of Dr. Mosher dated May 14, 2020 (SLVGT-EPA_0105503-513) - May 14, 2020 – Response of Final Office Action (SLVGT-EPA_0105519-532) - Aug. 3, 2020 – Notice of Allowance (SLVGT-EPA_0105656-663) <p><u>File History of '482 Patent</u></p> <ul style="list-style-type: none"> - Mar. 1, 2019 – Response to Non-Final Office Action (SLVGT-EPA_0105790-803) - Mar. 1, 2019 – Declaration of Dr. Mosher dated Feb. 2, 2017 (SLVGT-EPA_0105804-817) - Aug. 1, 2019 – Response to Final Office Action (SLVGT-EPA_0106721-728) - Oct. 24, 2019 – Response to Advisory Action and Final Office Action (SLVGT-EPA_0106753-760) - May 15, 2020 – Response to Non-Final Office Action (SLVGT-EPA_0106791-801) 	<p><u>'868 Patent Prosecution history</u></p> <p>Original claims at 48-51; Preliminary amendment dated January 18, 2019; Office Action dated May 2, 2019; August 1, 2019 Office Action Response; Declarations of Mosher dated February 2, 2017 and May 14, 2020; Office Action dated Nov 19, 2019; May 14, 2020 Office Action Response; Notice of Allowance dated August 8, 2020.</p> <p><u>'482 Patent Prosecution history</u></p> <p>Original claims at 48-51; Office Action dated January 25, 2019; March 1, 2019 Office Action Response; Declarations of Mosher dated February 2, 2017 and May 14, 2020; Office Action dated June 24, 2019; August 1, 2019 Office Action Response; Advisory Opinion dated September 16, 2019; October 24, 2019 Office Action Response; Office Action dated January 7, 2020; May 15, 2020 Office Action Response; Notice of allowance dated July 16, 2020.</p>

Claim Term	Corresponding Claims	Silvergate's Proposed Construction and Evidence	Bionpharma's Proposed Construction and Evidence
		<ul style="list-style-type: none"> - May 15, 2020 – Declaration of Dr. Mosher dated May 15, 2020 (SLVGT-EPA_0106802-808) - July 16, 2020 – Notice of Allowance (SLVGT-EPA_0106991-6999) <p><u>File History of '621 Patent</u></p> <ul style="list-style-type: none"> - Jan. 1, 2021 – Notice of Allowance (SLVGT-EPA_0107216-220) 	

EXHIBIT C

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US010772868B2

(12) **United States Patent**
Mosher et al.

(10) **Patent No.:** **US 10,772,868 B2**

(45) **Date of Patent:** ***Sep. 15, 2020**

(54) **ENALAPRIL FORMULATIONS**

(71) Applicant: **Silvergate Pharmaceuticals, Inc.**,
Greenwood Village, CO (US)

(72) Inventors: **Gerold L. Mosher**, Kansas City, MO
(US); **David W. Miles**, Kansas City,
MO (US)

(73) Assignee: **Silvergate Pharmaceuticals, Inc.**,
Greenwood Village, CO (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **16/242,898**

(22) Filed: **Jan. 8, 2019**

(65) **Prior Publication Data**

US 2019/0142797 A1 May 16, 2019

Related U.S. Application Data

(63) Continuation of application No. 16/177,159, filed on
Oct. 31, 2018, which is a continuation of application
No. 16/003,994, filed on Jun. 8, 2018, now Pat. No.
10,154,987, which is a continuation of application
No. 15/802,341, filed on Nov. 2, 2017, now Pat. No.
(Continued)

(51) **Int. Cl.**

A61K 31/401 (2006.01)
A61K 9/00 (2006.01)
A61K 47/26 (2006.01)
A61K 47/12 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 31/401** (2013.01); **A61K 9/0053**
(2013.01); **A61K 9/0095** (2013.01); **A61K**
47/12 (2013.01); **A61K 47/26** (2013.01)

(58) **Field of Classification Search**

CPC **A61K 31/401**; **A61K 47/12**; **A61K 47/26**;
A61K 9/0053; **A61K 9/0095**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,374,829 A 2/1983 Harris et al.
4,472,380 A 9/1984 Harris et al.
(Continued)

FOREIGN PATENT DOCUMENTS

CA 1275350 C 10/1990
EP 2903690 A1 8/2015
(Continued)

OTHER PUBLICATIONS

Sosnowska et al., "Stability of Extemporaneous Enalapril Maleate
Suspensions for Pediatric Use Prepared From Commercially Avail-
able Tablets", *Acta Poloniae Pharmaceutica—Drug Research*, 2009,
vol. 66, No. 3, pp. 321-326 (Year: 2009).*

(Continued)

Primary Examiner — Savitha M Rao

(74) *Attorney, Agent, or Firm* — Wilson, Sonsini,
Goodrich & Rosati, P.C.

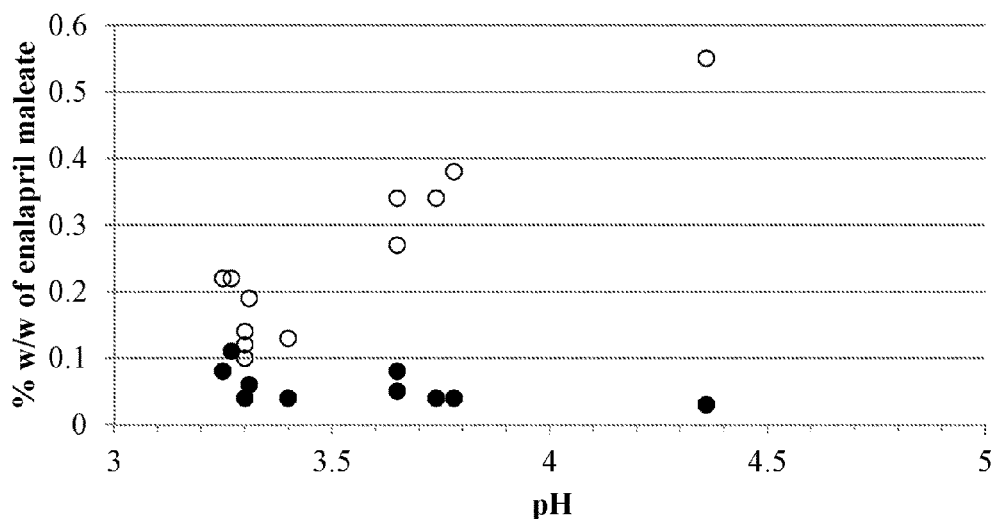
(57)

ABSTRACT

Provided herein are stable enalapril oral liquid formulations.
Also provided herein are methods of using enalapril oral
liquid formulations for the treatment of certain diseases
including hypertension, heart failure and asymptomatic left
ventricular dysfunction.

30 Claims, 2 Drawing Sheets

● Enalapril diketopiperazine; ○ Enalaprilat



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Related U.S. Application Data

10,039,745, which is a continuation of application No. 15/613,622, filed on Jun. 5, 2017, now Pat. No. 9,808,442, which is a continuation of application No. 15/081,603, filed on Mar. 25, 2016, now Pat. No. 9,669,008.

- (60) Provisional application No. 62/310,198, filed on Mar. 18, 2016.

(56) References Cited

U.S. PATENT DOCUMENTS

4,510,083	A	4/1985	Blacklock et al.
4,743,450	A	5/1988	Harris et al.
4,793,998	A	12/1988	Murthy et al.
4,830,853	A	5/1989	Murthy et al.
4,931,430	A	6/1990	Sudilovsky et al.
5,049,553	A	9/1991	Sudilovsky
5,698,562	A	12/1997	Mendes et al.
6,028,222	A	2/2000	Dietlin et al.
6,300,361	B1	10/2001	Vivilecchia et al.
6,300,362	B1	10/2001	Vivilecchia et al.
6,413,988	B1	7/2002	De Proost
6,509,350	B2	1/2003	Vivilecchia et al.
6,790,861	B2	9/2004	Vivilecchia et al.
6,869,963	B2	3/2005	Patel et al.
6,977,257	B2	12/2005	Parab et al.
7,101,888	B2	9/2006	Reo et al.
7,605,148	B2	10/2009	Batta et al.
8,153,824	B2	4/2012	Sesha
8,568,747	B1	10/2013	Rajewski et al.
8,778,366	B2	7/2014	Rajewski et al.
8,927,028	B2	1/2015	Grenier et al.
9,463,183	B1	10/2016	Mosher et al.
9,616,096	B1	4/2017	Mosher et al.
9,669,008	B1	6/2017	Mosher
9,808,442	B2	11/2017	Mosher
9,855,214	B2	1/2018	Rajewski
9,968,553	B1	5/2018	Rajewski
1,003,974	A1	8/2018	Mosher
1,015,498	A1	12/2018	Mosher et al.
2004/0171669	A1	9/2004	Chenevier
2004/0258757	A1	12/2004	Bosch et al.
2006/0094760	A1	5/2006	Fawzy et al.
2006/0121066	A1	6/2006	Jaeger et al.
2007/0265344	A1	11/2007	Strobel et al.
2008/0221156	A1	9/2008	Spireas
2008/0234291	A1	9/2008	Francois et al.
2009/0269287	A1	10/2009	Berta
2010/0222334	A1	9/2010	Talamonti et al.
2011/0003798	A1	1/2011	Okram et al.
2014/0100260	A1	4/2014	Rajewski et al.
2015/0148335	A1	5/2015	Bova et al.
2015/0258027	A1	9/2015	Rajewski et al.
2017/0119840	A1	5/2017	Mosher et al.
2017/0209523	A1	7/2017	Mosher et al.
2017/0266159	A1	9/2017	Mosher et al.
2018/0055821	A1	3/2018	Mosher et al.

FOREIGN PATENT DOCUMENTS

WO	WO-9814196	A1	4/1998
WO	WO-9930690	A1	6/1999
WO	WO-1999030690		6/1999
WO	WO-0145667	A2	6/2001
WO	WO-02089775	A1	11/2002
WO	WO-2007070843	A2	6/2007
WO	WO-2009116078	A2	9/2009
WO	WO-2011031462	A2	3/2011
WO	WO-2011128783	A2	10/2011
WO	WO-2012085249	A2	6/2012
WO	WO-2014055667	A1	4/2014
WO	WO-2014178065	A1	11/2014
WO	WO-2017075368	A1	5/2017
WO	WO-2017161339	A1	9/2017

OTHER PUBLICATIONS

Boukarim et al., "Preservatives in Liquid Pharmaceutical Preparations", J. Appl. Res., 2009, vol. 9, No. 1&2, pp. 14-17 (Year: 2009).*

Parish, "How do salt and sugar prevent microbial spoilage?", Scientific American, 2006 (Year: 2006).*

AAPS American Association of Pharmaceutical Scientists, Preliminary Program, 2011 AAPS Annual Meeting and Exposition, Washington, D.C., Oct. 23-27, 2011, 112 pages.

Ahlin et al. Investigation of polymeric nanoparticles as carriers of enalaprilat for oral administration. Int'l. J. Pharmaceutics 239:113-120 (2002).

Allen et al. Stability of alprazolam, chloroquine phosphate, cispapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids. Am J. Health-Syst Pharm 55:1915-1920 (1998).

Allen. Lisinopril 1 mg/mL oral liquid US Pharm. 38(2):36-37 (2013).

Al-Omari et al. Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations. Journal of Pharmaceutical and Biomedical Analysis 25:893-902 (2001).

Bhardwaj et al. Study of forced degradation behavior of enalapril maleate by LC and LC-MS and development of a validated stability-indicating assay method. Journal of Pharmaceutical and Biomedical Analysis 46:113-120 (2008).

Blowey. Update on the pharmacologic treatment of hypertension in pediatrics. Journal of Clinical Hypertension 14(6), 383-387 (2012).

Boukarim et al. Preservatives in liquid pharmaceutical preparations. The Journal of Applied Research 9(1 & 2):14-17 (2009).

Bourgault et al., Reference-based pricing of prescription drugs: exploring the equivalence of angiotensin-converting-enzyme inhibitors. CMAJ 161:255-60 (1999).

Brilla et al., Lisinopril-Mediated regression of myocardial fibrosis in patients with hypertensive heart disease. Circulation 102:1388-1393 (2000).

Cabot Corporation, "Influence of CAB-O-SIL® M-5P on the Angle of Repose and Flow Rates of Pharmaceutical Powders," 10 pages (2004).

Calabro et al. Hemodynamic effects of a single oral dose of enalapril among children with asymptomatic chronic mitral regurgitation. American Heart Journal 138(5, Pt. 1):955-961 (1999).

Definition of Hypertension (1 page) retrieved from: <http://medical-dictionary.thefreedictionary.com/hypertension> (2008).

Delucchi et al., "Enalapril and prednisone in children with nephrotic-range proteinuria," Pediatric nephrology (Berlin, Germany) (2000), 14(12), 1088-91, Database: MEDLINE.

Drug Information on Enalapril (3 pages), 2001. retrieved from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/18-998s058_Vasotec.cfm.

drugs.com. Enalapril Tablets Soluble. Website [online]. [available online May 9, 2010] [retrieved on Jan. 16, 2014], 11 pages. Retrieved from the Internet< URL: <https://web.archive.org/web/20100509220009/http://www.drugs.com/pro/enalapril-tablets-soluble.html>>. Enalapril Tablets Soluble-Clinical Pharmacology; Indications and Usage for Enalapril Tablets Soluble; Enalapril Tablets Soluble Dosage and Administration.

Glass et al. Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. J Pharm Sci 9(3):398-426 (2006).

Gulf Cooperation Council. The GCC Guidelines for Stability Testing of Drug Substances and Pharmaceutical Products. Publication [online]. Edition Two, 1428 H-2007 G [available online Jul. 2011] [retrieved on Feb. 3, 2014]. Retrieved from the Internet:< URL: https://web.archive.org/web/20110726040053/http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisation/GCC/T_opics_under_Harmonisation/Stability.pdf>. p. 22, 2.9.3; p. 25, 2.9.7.

Handbook of Pharmaceutical Excipients, Fifth edition, edited by Raymond C. Rowe et al., London: Pharmaceutical Press, 2006, (monographs for citric acid monohydrate, sodium benzoate, sodium citrate, sodium hydroxide, and xylitol), 23 pages.

US 10,772,868 B2

Page 3

(56)

References Cited

OTHER PUBLICATIONS

Harris, Daniel C. Exploring Chemical Analysis, 4th edition. New York: W.H. Freeman and Company, 2009 (Chapters 8, 9, 21 and 22), 105 pages.

Hensel et al. Transesterification reactions off parabens (Alkyl 4-Hydroxybenzoates) with polyols in aqueous solution. *J Pharm Sci* 84(1):115-119 (1995).

Hsu et al. Enalapril in Infants With Single Ventricle: Results of a Multicenter Randomized Trial. *Circulation* 122(4):333-340 (2010).

Hsu et al. Rationale and design of a trial of angiotensin-converting enzyme inhibition in infants with single ventricle. *American Heart Journal* 157(1):37-45 (2009).

Kalaitzidis et al. Prehypertension: is it relevant for nephrologists? *Kidney International* 77:194-200 (2010).

Li et al. Lessons learned from a pediatric clinical trial: The Pediatric Heart Network Angiotensin-Converting Enzyme Inhibition in Mitral Regurgitation Study. *American Heart Journal* 161(2):233-240 (2011).

Lima et al., "Stability and in vitro release profile of enalapril maleate from different commercially available tablets: Possible therapeutic implications," *Journ. Pharmac. and Biomed. Analysis*, 47, pp. 934-937 (2008).

Lipshultz, "Exposure to anthracyclines during childhood causes cardiac injury," *Seminars in Oncology* (2006), 33(3, Suppl. 8), S8-S14., Database: CAPLUS, DOI:10.1053/j.seminoncol.2006.04.019.

Ma et al., HPLC and LC-MS studies of the transesterification reaction of Methylparaben with twelve 3-to 6-carbon sugar alcohols and propylene glycol and the isomerization of the reaction products by acyl migration. *Journal of Chromatographic Science*, 40(3):170-177, 2002.

Meyers et al. Pharmacotherapy Review of Chronic Pediatric Hypertension. *Clinical Therapeutics* (2011), 33(10), 1331-1356. Database: CAPLUS, DOI:10.1016/j.clinthera.2011.09.003.

Miller et al., "Enalapril: a well-tolerated and efficacious agent for the paediatric hypertensive patient," *Journal of hypertension. Supplement : official journal of the International Society of Hypertension* (1986), 4(5), S413-6, Database: MEDLINE.

Miller et al., "Enalapril: a well-tolerated and efficacious agent for the pediatric hypertensive patient," *Journal of cardiovascular pharmacology* (1987), 10 Suppl 7S154-6, Database: MEDLINE.

Mir et al., "Effect of carvedilol on QT duration in pediatric patients with congestive heart failure," *Clinical Drug Investigation* (2004), 24(1), 9-15. Database: CAPLUS, DOI:10.2165/00044011-200424010-00002.

Momma, "ACE inhibitors in pediatric patients with heart failure," *Paediatric drugs* (2006), 8(1), 55-69, Database: MEDLINE.

Nahata et al. Stability of enalapril maleate in three extemporaneously prepared oral liquids. *Am. J. Health-Syst Pharm* 55:1155-1157 (1998).

Nakamura et al., "The kinetic profiles of enalapril and enalaprilat and their possible developmental changes in pediatric patients with congestive heart failure," *Clinical pharmacology and therapeutics* (1994), 56(2), 160-8, Database: MEDLINE.

National Institutes of Health. 'MedlinePlus: Hypertension'. Website [online]. [available online May 20, 2012] [retrieved on Jan. 16, 2014], 5 pages. Retrieved from the Internet: <URL:https://web.archive.org/web/20120520035026/http://www.nlm.nih.gov/medlineplus/ency/article/000468.htm>.

Nationwide Children's Hospital. 'Enalapril Oral Suspension' Publication [online]. Mar. 29, 2010 [retrieved on Jan. 14, 2014], 1 page. Retrieved from the Internet: <URL:http://www.nationwidechildrens.org/Document/Get/78785>.

Niazi, Sarfaraz K. Handbook of Pharmaceutical Manufacturing Formulations: Liquid Products, vol. 3, Second edition. New York: Informa Healthcare USA, Inc., 2009, 400 pages.

Nicolosi et al., The prognostic value of predischARGE quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 trial. *European Heart Journal*, 17:1646-1656, 1996.

Novartis AG (Appellants) v. Torrent Pharmaceuticals Limited, Apotex Inc., Mylan Pharmaceuticals Inc., (Appellees), No. 2016-1352, Slip Opinion decided Apr. 12, 2017, 27 pages.

Nunn et al. Formulation of medicines for children. *British Journal of Clinical Pharmacology*, 59:6, pp. 674-676 (2005).

Packer et al., Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation*, 100:2312-1218, 1999.

Patel et al., "Extemporaneous Dosage Form for Oral Liquids," *Pharmacophore*, vol. 2, No. 2, pp. 86-103 (2011).

PCT Patent Application No. PCT/US2016/059348 International Search Report and Written Opinion dated Jan. 3, 2017.

PCT Patent Application No. PCT/US2017/023074 International Search Report and Written Opinion dated Jun. 16, 2017.

Product Information of Bicitra, "Sodium Citrate and Citric Acid Oral Solution USP." 2 pages.

Product Information of Ora-Sweet(1 page, 2013) retrieved from, <http://www.stobec.com/documents/data/8196.pdf>.

Proesmans et al., "Enalapril in children with Alport syndrome," *Pediatric nephrology* (Berlin, Germany) (2004), 19(3), 271-5, Database: MEDLINE.

Proesmans et al., Long-term therapy with enalapril in patients with nephrotic-range proteinuria, *Pediatric nephrology* (Berlin, Germany) (1996), 10(5), 587-9, Database: MEDLINE.

Proesmans et al., "Enalapril in pediatric patients with Alport syndrome: 2 years' experience," *European Journal of Pediatrics* (2000), 159(6), 430-433. Database: CAPLUS, DOI:10.1007/s004310051301.

Raia, et al., Angiotensin-converting enzyme inhibitors: A Comparative review. *DPIC, The Annals of Pharmacotherapy*, 24:506-525, 1990.

Ramusovic et al., "Determination of enalapril and enalaprilat in small human serum quantities for pediatric trials by HPLC-tandem mass spectrometry," *Biomedical Chromatography* (2012), 26(6), 697-702. Database: CAPLUS, DOI:10.1002/bmc.1716.

Rezende et al., "Stability and Compatibility Study on Enalapril Maleate Using Thermoanalytical Techniques," *Journ Thermal Analysis and Calorimetry*, 93:3, pp. 881-886 (2008).

Rose et al., Stability of Lisinopril syrup (2 mg/mL) extemporaneously compounded from tablets. *Int J Pharm Compd*. 4(5):398-399 (2000).

Russell, Craig Allen, Paediatric Drug Development:— Reformulation, in Vitro, Genomic and in Vivo Evaluation. Thesis, Apr. 2014, 330 pages.

Schlatter et al., Stability of Enalapril solutions prepared from tablets in sterile water. *Australian J. Hospital Pharmacy*, 27:395, 1997.

Seikaly. Hypertension in children: an update on treatment strategies. *Current Opinion in Pediatrics*, 19:170-177, 2007.

Silber et al., "Design and baseline characteristics for the ACE inhibitor after anthracycline (AAA) study of cardiac dysfunction in long-term pediatric cancer survivors," *American Heart Journal* (2001), 142(4), 577-585. Database: CAPLUS, DOI:10.1067/mhj.2001.118115.

Silber et al., "Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines," *Journal of Clinical Oncology* (2004), 22(5), 820-828. Database: CAPLUS, DOI:10.1200/JCO.2004.06.022.

Simončič et al., "Use of microcalorimetry in determination of stability of enalapril maleate and enalapril maleate table formulations," *Int'l. Journ. Pharmaceutics*, 342, pp. 145-151 (2007).

Sipahi et al. Effect of Antihypertensive Therapy on Incident Stroke in Cohorts with Prehypertensive Blood Pressure Levels: A Meta-Analysis of Randomized Controlled Trials, *Stroke: Journal of the American Heart Association* [online], Dec. 8, 2011 [retrieved Jan. 16, 2014]. 10 pages. Retrieved from the Internet: <URL:http://www.medpagetoday.com/upload/2011/12/9/Stroke-2011-Sipahi-STROKEAHA.111.636829.pdf>.

Sipahi et al., Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis, *J. Am. Coll. Cardiol*. 48, 833-838, 2006.

Garrett. Prediction of stability of drugs and pharmaceutical preparations. *Journal of Pharmaceutical Sciences* 51(9):811-833 (1962).

US 10,772,868 B2

Page 4

(56)

References Cited

OTHER PUBLICATIONS

Standing et al. Paediatric formulations—Getting to the heart of the problem. *International Journal of Pharmaceutics* (2005), 300(1-2), 56-66. Database: CAPLUS.

Stanisz, "Evaluation of stability of enalapril maleate in solid phase," *Journ. Pharma. and Biomed. Analysis*, 31, pp. 375-380 (2003).

TEVA UK, Limited. Enalapril Maleate 2.5 mg, 5 mg, 10 mg and 20 mg Tablets. Product Brochure [online]. Mar. 2011 [retrieved on Jan. 14, 2014], 8 pages. Retrieved from the Internet:<URL:http://www.drugs.com/uk/pdf/leaflet/213793.pdf>. col. 2, lines 70-76.

Thompson et al., Characterization of an extemporaneous liquid formulation of lisinopril. *Am J Health Syst Pharm*. 60(1):69-74 (2003).

Tian et al., Effect of organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphism on the single- and multiple-dose pharmacokinetics of enalapril in healthy Chinese adult men *Clinical Therapeutics*, 33(5): 655 (2011).

U.S. Appl. No. 13/670,355 Office Action dated Feb. 8, 2013.

U.S. Appl. No. 13/670,355 Office Action dated Jul. 30, 2013.

U.S. Appl. No. 13/914,452 Office Action dated Aug. 28, 2013.

U.S. Appl. No. 14/433,502 Office Action dated Dec. 29, 2016.

U.S. Appl. No. 14/433,502 Restriction Requirement dated Apr. 12, 2016.

U.S. Appl. No. 14/934,752 First Action Interview dated Jan. 25, 2016.

U.S. Appl. No. 14/934,752 Office Action dated Apr. 26, 2016.

U.S. Appl. No. 15/081,603 First Action Interview dated Sep. 2, 2016.

U.S. Appl. No. 15/081,603 First Action Interview Office Action Summary dated Jan. 17, 2017.

U.S. Appl. No. 15/268,095 Office Action dated Oct. 13, 2016.

U.S. Appl. No. 15/433,743 Office Action dated Jun. 5, 2017.

U.S. Appl. No. 15/613,622 Office Action dated Aug. 11, 2017.

U.S. Appl. No. 15/850,732 Office Action dated Mar. 1, 2018.

U.S. Appl. No. 16/003,994 Office Action dated Sep. 20, 2018.

U.S. Appl. No. 15/802,341 Office Action dated Apr. 19, 2018.

Van Hecken et al. Absence of a pharmacokinetic interaction between enalapril and frusemide *British Journal of Clinical Pharmacology*, 1987, vol. 23:84-87.

VASOTEC (Enalapril Maleate) Product Insert (2010) 5 pages.

Wang et al., "Eudragit E Accelerated the Diketopiperazine Formation of Enalapril Maleate Determined by Thermal FTIR Microspectroscopic Technique," *Pharmaceutical Research*, vol. 21, No. 11, Nov. 2004.

Webster et al., The Stability of Lisinopril as an extemporaneous syrup. *Int J Pharm Compd*. 1(5):352-353 (1997).

Wells et al., "A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension," *Journal of Clinical Pharmacology* (2002), 42(8), 870-880. Database: CAPLUS, DOI:10.1177/009127002401102786.

Wells et al., "The Pharmacokinetics of Enalapril in Children and Infants with Hypertension," *J. Clin Pharmacol* 41:1064-1074 (2001).

Williams et al., "Factors affecting growth in infants with single ventricle physiology: a report from the Pediatric Heart Network Infant Single Ventricle Trial," *The Journal of Pediatrics* (2011), 159(6), 1017-22.e2, Database: MEDLINE.

European Patent Application No. 13844343.7 Extended European Search Report dated Feb. 19, 2016.

Liern et al., The additive antiproteinuric effect of Enalapril and Losartan to normotensive patients with pathology proteinuria, *Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia* (2004), 24(6), 553-8, Database: MEDLINE (with English abstract).

PCT Patent Application No. PCT/US2013/063096 International Search Report dated Feb. 20, 2014.

PCT Patent Application No. PCT/US2013/063096 Written Opinion dated Feb. 20, 2014.

PCT/US2013/63096 International Preliminary Report on Patentability dated Apr. 7, 2015.

Sandoz, Limited. Amoxicillin 125 mg/5 ml Powder for Oral Suspension'. Product brochure [online]. Jul. 2012 [retrieved on Jan. 17, 2014]. Retrieved from the Internet<URL:http://www.drugs.com/uk/pdf/leaflet/196044.pdf>.

Sosnowska et al., Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared from Commercially Available Tablets, *Acta Poloniae Pharmaceutica*, vol. 66, No. 3, pp. 321-326 (2009).

U.S. Appl. No. 15/483,691 Office Action dated Jun. 8, 2017.

U.S. Appl. No. 16/177,159 Final Office Action dated Jun. 24, 2019.

Al-Omari, M.M. et al., Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations, *J. of Pharmaceutical and Biomedical Analysis* 25 (2001) 893-902.

Casas, Marta et al., Physicochemical stability of captopril and enalapril extemporaneous formulations for pediatric patients, *Pharm Dev Technol*, 2015; 20(3): 271-278.

European Search Report for EP17767676.4 dated Oct. 8, 2019.

Extended European Search Report dated Feb. 19, 2016, for EP Application No. 13844343.7.

International Search Report and Written Opinion dated Jun. 16, 2017 for PCT/US17/023074.

Mc Nahata et al., Stability of enalapril maleate in three extemporaneously prepared oral liquids, *American Journal of Health System Pharmacy*, American Society of Healthy Systems Pharmacy, US, vol. 55, No. 11, Jun. 1, 1998, pp. 1155-1157.

Nationwide Children's Hospital Pharmacy, Columbus, Ohio, Enalapril Oral Suspension Dosage Form, Mar. 29, 2010, XP055291016.

Non-Final Office Action dated Jan. 7, 2019, for U.S. Appl. No. 16/177,159.

Ripley et al., "Pharmacokinetic Assessment of an Oral Enalapril Suspension for Use in Children," *Biopharmaceutics & Drug Disposition* 21:339-344 (2000).

Silvergate Pharmaceuticals, Inc. (Plaintiff) v. Bionpharma, Inc. (Defendant) C.A. No. 1:16-cv-00876-SLR (consolidated). Bionpharma Inc.'s Invalidity Contentions Pursuant to Delaware Default Standard Rule 4(d). Jun. 9, 2017, 50 pages.

U.S. Appl. No. 16/177,159 Advisory Action dated Sep. 16, 2019.

* cited by examiner

U.S. Patent

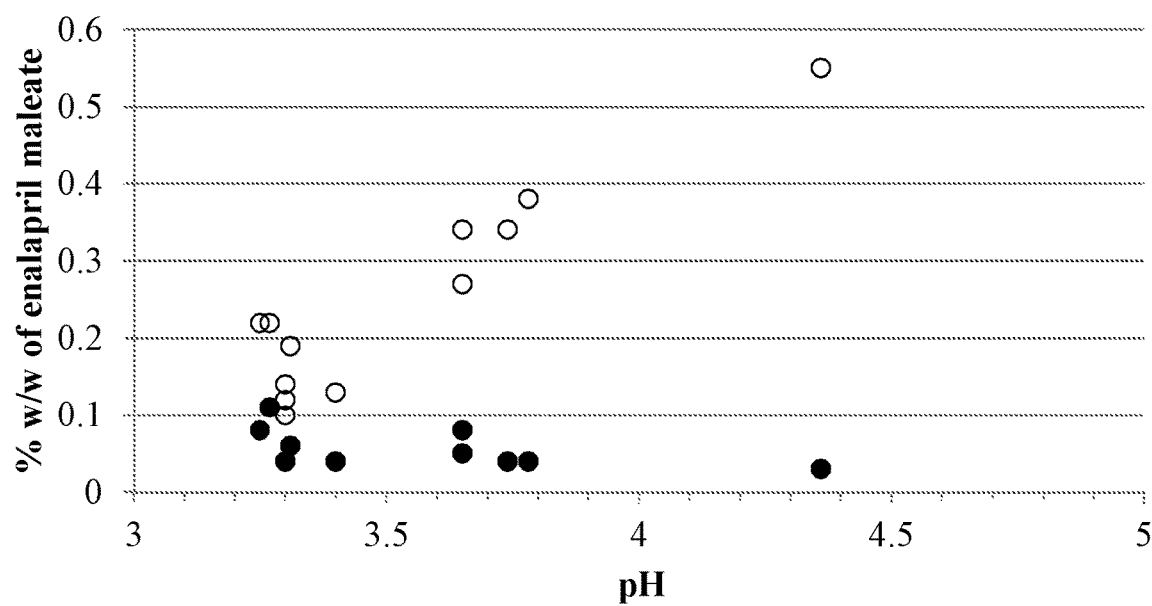
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FIG. 1

● Enalapril diketopiperazine; ○ Enalaprilat



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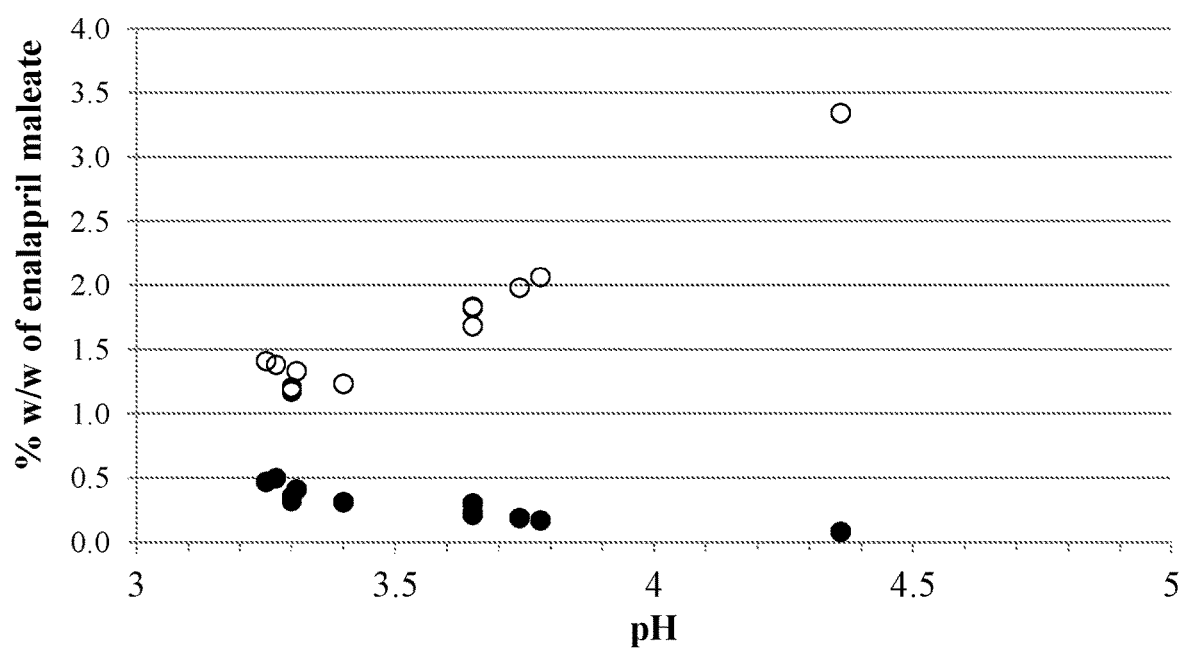
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FIG. 2

● Enalapril diketopiperazine; ○ Enalaprilat



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ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

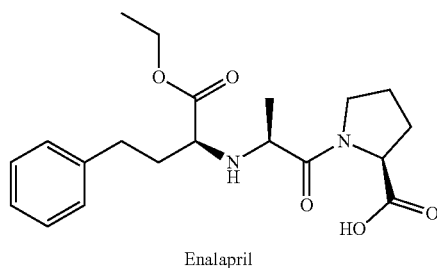
This application is a continuation of U.S. patent application Ser. No. 16/177,159, filed Oct. 31, 2018, which is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018, which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

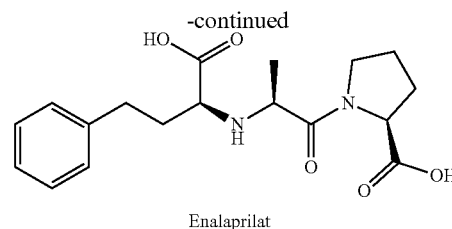
Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineral corticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



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Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water;

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wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an

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adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed descrip-

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tion that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treat-

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ment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83

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mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodi-

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ments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005—maltodextrin, sorbitol, and fructose combination and Product Code 918.010—water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), Maltisweet™ (maltitol solution, Ingredient), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn

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syrup, Ingredient), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155

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mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32

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mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5%

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w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2%

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w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and Preservative Incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

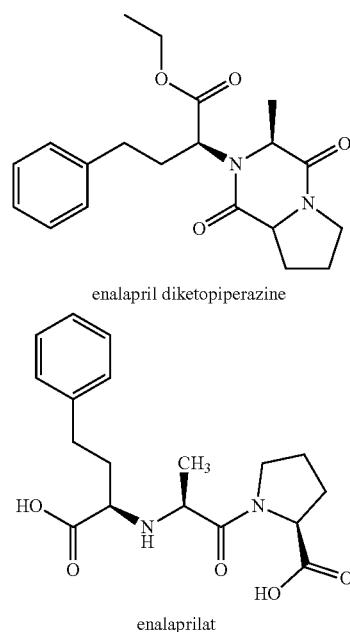
In some embodiments, the oral liquid formulation comprises a buffer.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:

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In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml,

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about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1 mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34%

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w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1% w/w to about 5% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5% w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/mL, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the

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oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1% w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, *eucalyptus*, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise,

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cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry.

In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18

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months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is $5\pm 3^\circ\text{C}$. In some embodiments, refrigerated condition is about 2°C ., about 2.1°C ., about 2.2°C ., about 2.3°C ., about 2.4°C ., about 2.5°C ., about 2.6°C ., about 2.7°C ., about 2.8°C ., about 2.9°C ., about 3°C ., about 3.1°C ., about 3.2°C ., about 3.3°C ., about 3.4°C ., about 3.5°C ., about 3.6°C ., about 3.7°C ., about 3.8°C ., about 3.9°C ., about 4°C ., about 4.1°C ., about 4.2°C ., about 4.3°C ., about 4.4°C ., about 4.5°C ., about 4.6°C ., about 4.7°C ., about 4.8°C ., about 4.9°C ., about 5°C ., about 5.1°C ., about 5.2°C ., about 5.3°C ., about 5.4°C ., about 5.5°C ., about 5.6°C ., about 5.7°C ., about 5.8°C ., about 5.9°C ., about 6°C ., about 6.1°C ., about 6.2°C ., about 6.3°C ., about 6.4°C ., about 6.5°C ., about 6.6°C ., about 6.7°C ., about 6.8°C ., about 6.9°C ., about 7°C ., about 7.1°C ., about 7.2°C ., about 7.3°C ., about 7.4°C ., about 7.5°C ., about 7.6°C ., about 7.7°C ., about 7.8°C ., about 7.9°C ., or about 8°C . At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. $25\pm 5^\circ\text{C}$.; $55\pm 10\%$ RH). In some instances, an accelerated condition is at about 25°C ., about 30°C ., about 35°C ., about 40°C ., about 45°C ., about 50°C ., about 55°C ., or about 60°C . In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40°C ., or 60°C ., at ambient humidity. In yet further instances, an accelerated condition is about 40°C ., at $75\pm 5\%$ RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about

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15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and

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the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for an enalapril oral liquid formulation. In other

embodiments, a syrup is used for as a vehicle for an enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for an enalapril oral liquid formulation. Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate. In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, *eucalyptus*, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and

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mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof, and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the

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liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2x10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

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Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset

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of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of

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about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76 mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet

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formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does not improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to

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a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxyben-

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zamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartin, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

“Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

“Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

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The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms “patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of

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the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at 60° C.	Formulation					
	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07

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TABLE A-2-continued

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at 60° C.	Formulation					
	A1	A2	A3	A4	A5	A6
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5

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TABLE B-1-continued

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours at 60° C.	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

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TABLE C-1

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)								
40	Storage		Formulation					
	° C.	Weeks	C1	C2	C3	C4	C5	
Liquid Formulations								
45	Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
			4	0.02	0.03	0.03	0.03	0.02
			8	0.03	0.04	0.04		
		19-23	0	0.03	0.04	0.04	0.02	0.02
	4		0.05	0.09	0.11	0.05	0.04	
	8		0.08	0.17	0.19			
	50	40	0	0.03	0.04	0.04	0.02	0.02
			4	0.35	0.91	1.10	0.31	0.21
8			0.65	1.80	2.05			
Enalaprilat		5	0	0.18	0.14	0.12	0.13	0.19
	4		0.18	0.15	0.12	0.43	0.53	
	8		0.55	0.38	0.34			
	19-23	0	0.18	0.14	0.12	0.13	0.19	
		4	1.35	0.83	0.80	1.75	2.29	
		8	3.34	2.06	1.98			
	40	0	0.18	0.14	0.12	0.13	0.19	
		4	10.49	6.08	6.11	12.30	16.14	
8		24.37	14.12	14.22				

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar

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and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with

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additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations						
Component	D1	D2	D3	D4	D5	D6
Powder Formulation (grams)						
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

40 The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)								
		Storage		Formulation				
		° C.	Weeks	D1	D2	D3	D4	D5
Liquid Formulations								
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		

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TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	° C.	Weeks	D1	D2	D3	D4	D5	D6
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
	19-23	8	0.32	0.30	0.30	0.39		
		0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
	40	12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		
		0	0.03	0.02	0.03	0.03	0.13	0.14
		4	4.76	4.42	4.76	6.45	5.55	5.24
		8	8.95	8.64	9.61	12.94	12.73	12.18
		12	11.01	10.64	11.41	16.16		
		26	17.18	17.11	18.30	27.36		

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Example E: Stability of Solution Formulations of
Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		

-continued

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	° C.	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
	19-23	62	0.18	0.18	0.16	0.14		
		0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28
		12	0.58	0.59	0.53	0.51	0.48	0.45
		26	1.10	1.10	1.00	0.95	0.97	0.92
	40	52					2.30	2.15
		62	3.02	3.04	2.75	2.64		
		0	0.01	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76	1.68
		8	4.02	3.99	3.99	3.62	3.37	3.13
		12	6.72	6.42	6.47	6.00	5.53	5.29
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11

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TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Storage		Formulation					
° C.	Weeks	E1	E2	E3	E4	E5	E6
19-23	26	0.31	0.30	0.29	0.31	0.27	0.24
	52					0.54	0.46
	62	0.75	0.75	0.74	0.71		
	0	0.00	0.00	0.01	0.02	0.00	0.00
	4	0.65	0.65	0.68	0.70	0.50	0.46
	8	1.17	1.19	1.20	1.23	1.03	0.95
	12	1.67	1.69	1.72	1.80	1.30	1.21
	26	3.36	3.38	3.42	3.57	3.07	2.90
	52					6.32	5.88
	62	7.99	8.02	8.04	8.57		
40	0	0.00	0.00	0.01	0.02	0.00	0.00
	4	4.85	4.93	5.19	5.42	3.33	3.25
	8	8.08	8.06	8.56	9.01	6.65	6.35
	12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. 1 (5° C. ±3° C.) and FIG. 2 (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

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Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution Vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of

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variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_m were approximately 115% and 109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A stable oral liquid formulation, consisting essentially of:

- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;
- wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
- wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months; and
- wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

2. The stable oral liquid formulation of claim 1, comprising a sweetener.

3. The stable oral liquid formulation of claim 2, wherein the sweetener is sucralose.

4. The stable oral liquid formulation of claim 1, comprising a flavoring agent.

5. The stable oral liquid formulation of claim 1, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, or a tartrate buffer.

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6. The stable oral liquid formulation of claim 1, wherein the buffer comprises citric acid and sodium citrate.

7. The stable oral liquid formulation of claim 6, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.

8. The stable oral liquid formulation of claim 1, wherein the buffer concentration is about 10 mM to about 20 mM.

9. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH between about 3 and about 4.

10. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH at about 3.3.

11. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 18 months.

12. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 24 months.

13. A stable oral liquid formulation, consisting essentially of:

- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
- (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
- (iv) water;

wherein the formulation comprises a sweetener and a flavoring agent, wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

14. A stable oral liquid formulation, comprising consisting essentially of:

- (i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
- (iii) about 19% (w/w of solids) of a preservative that is sodium benzoate; and
- (iv) water;

wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;

wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

15. The stable oral liquid formulation of claim 14, comprising a sweetener.

16. The stable oral liquid formulation of claim 15, wherein the sweetener is sucralose.

17. The stable oral liquid formulation of claim 14, comprising a flavoring agent.

18. The stable oral liquid formulation of claim 14, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.

19. The stable oral liquid formulation of claim 14, wherein the buffer comprises citric acid and sodium citrate.

20. The stable oral liquid formulation of claim 19, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.

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21. The stable oral liquid formulation of claim 14, wherein the buffer concentration is about 10 mM to about 20 mM.

22. The stable oral liquid formulation of claim 14, wherein the buffer maintains the pH between about 3 and about 3.5.

23. The stable oral liquid formulation of claim 14, wherein the buffer maintains the pH at about 3.3.

24. The stable oral liquid formulation of claim 14, wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months.

25. The stable oral liquid formulation of claim 14, wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months.

26. A stable oral liquid formulation, consisting essentially of:

- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a citrate buffer to maintain the pH about 4.5 or below comprising citric acid and sodium citrate;
- (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
- (iv) water;

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wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;

wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

27. The stable oral liquid formulation of claim 26, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.

28. The stable oral liquid formulation of claim 1, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.

29. The stable oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.

30. The stable oral liquid formulation of claim 1, wherein the buffer comprises a buffer selected from a citrate, a phosphate, a citrate/phosphate, an acetate, a tartrate, a lactate, a glycinate, and an amino acid buffer.

* * * * *



US010786482B2

(12) **United States Patent**
Mosher et al.

(10) **Patent No.:** **US 10,786,482 B2**

(45) **Date of Patent:** ***Sep. 29, 2020**

(54) **ENALAPRIL FORMULATIONS**

(71) Applicant: **Silvergate Pharmaceuticals, Inc.**,
Greenwood Village, CO (US)

(72) Inventors: **Gerold L. Mosher**, Kansas City, MO
(US); **David W. Miles**, Kansas City,
MO (US)

(73) Assignee: **SILVERGATE**
PHARMACEUTICALS, INC.,
Greenwood Village, CO (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **16/177,159**

(22) Filed: **Oct. 31, 2018**

(65) **Prior Publication Data**
US 2019/0070147 A1 Mar. 7, 2019

Related U.S. Application Data

(63) Continuation of application No. 16/003,994, filed on
Jun. 8, 2018, now Pat. No. 10,154,987, which is a
continuation of application No. 15/802,341, filed on
Nov. 2, 2017, now Pat. No. 10,039,745, which is a
continuation of application No. 15/613,622, filed on
(Continued)

(51) **Int. Cl.**
A61K 31/401 (2006.01)
A61K 9/00 (2006.01)
A61K 47/26 (2006.01)
A61K 47/12 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 31/401** (2013.01); **A61K 9/0053**
(2013.01); **A61K 9/0095** (2013.01); **A61K**
47/12 (2013.01); **A61K 47/26** (2013.01)

(58) **Field of Classification Search**

CPC **A61K 31/401**; **A61K 47/12**; **A61K 47/26**;
A61K 9/0053; **A61K 9/0095**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,374,829 A 2/1983 Harris et al.
4,472,380 A 9/1984 Harris et al.
(Continued)

FOREIGN PATENT DOCUMENTS

CA 1275350 C 10/1990
EP 2903690 A1 8/2015
(Continued)

OTHER PUBLICATIONS

Nahata et al., "Stability of enalapril maleate in three extemporane-
ously prepared oral liquids", Am. J. Health-Syst. Pharm., 1998, vol.
55, pp. 1155-1157 (Year: 1998).*

(Continued)

Primary Examiner — Savitha M Rao

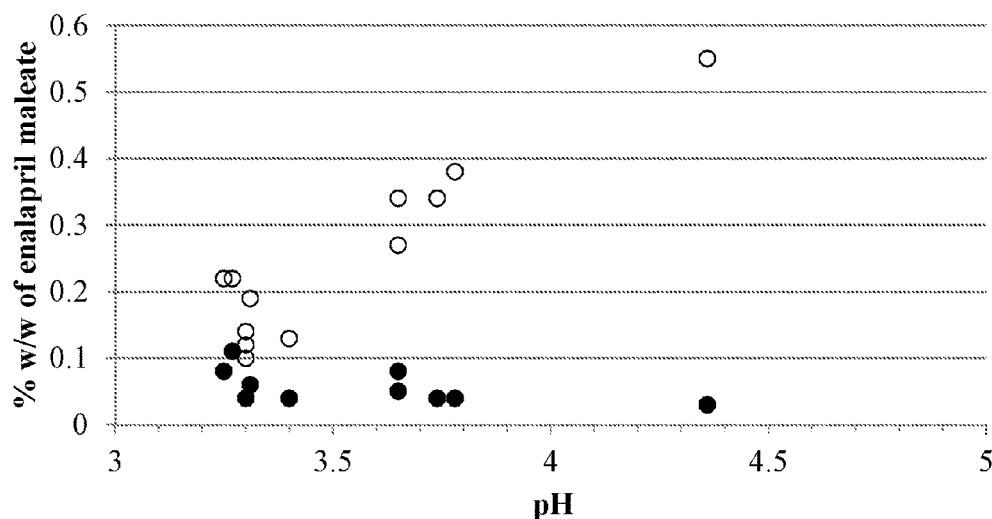
(74) *Attorney, Agent, or Firm* — Wilson, Sonsini,
Goodrich & Rosati, P.C.

(57) **ABSTRACT**

Provided herein are stable enalapril oral liquid formulations.
Also provided herein are methods of using enalapril oral
liquid formulations for the treatment of certain diseases
including hypertension, heart failure and asymptomatic left
ventricular dysfunction.

28 Claims, 2 Drawing Sheets

● Enalapril diketopiperazine; ○ Enalaprilat



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Related U.S. Application Data

Jun. 5, 2017, now Pat. No. 9,808,442, which is a continuation of application No. 15/081,603, filed on Mar. 25, 2016, now Pat. No. 9,669,008.

- (60) Provisional application No. 62/310,198, filed on Mar. 18, 2016.

(56) References Cited

U.S. PATENT DOCUMENTS

4,510,083	A	4/1985	Blacklock et al.
4,743,450	A	5/1988	Harris et al.
4,793,998	A	12/1988	Murthy et al.
4,830,853	A	5/1989	Murthy et al.
4,931,430	A	6/1990	Sudilovsky et al.
5,049,553	A	9/1991	Sudilovsky
5,698,562	A	12/1997	Mendes et al.
6,028,222	A	2/2000	Dietlin et al.
6,300,361	B1	10/2001	Vivilecchia et al.
6,300,362	B1	10/2001	Vivilecchia et al.
6,413,988	B1	7/2002	De
6,509,350	B2	1/2003	Vivilecchia et al.
6,790,861	B2	9/2004	Vivilecchia et al.
6,869,963	B2	3/2005	Patel et al.
6,977,257	B2	12/2005	Parab et al.
7,101,888	B2	9/2006	Reo et al.
7,605,148	B2	10/2009	Batta et al.
8,153,824	B2	4/2012	Sesha
8,568,747	B1	10/2013	Rajewski et al.
8,778,366	B2	7/2014	Rajewski et al.
8,927,028	B2	1/2015	Grenier et al.
9,463,183	B1	10/2016	Mosher et al.
9,669,008	B1	6/2017	Mosher
9,808,442	B2	11/2017	Mosher
9,855,214	B2	1/2018	Rajewski
9,968,553	B1	5/2018	Rajewski
10,039,745	B2	8/2018	Mosher
2004/0171669	A1	9/2004	Chenevier
2004/0258757	A1	12/2004	Bosch et al.
2006/0094760	A1	5/2006	Fawzy et al.
2006/0121066	A1	6/2006	Jaeger et al.
2007/0265344	A1	11/2007	Strobel et al.
2008/0221156	A1	9/2008	Spireas
2008/0234291	A1	9/2008	Francois et al.
2009/0269287	A1	10/2009	Berta
2010/0222334	A1	9/2010	Talamonti et al.
2011/0003798	A1	1/2011	Okram et al.
2014/0100260	A1	4/2014	Rajewski et al.
2015/0148335	A1	5/2015	Bova et al.
2015/0258027	A1	9/2015	Rajewski
2017/0266159	A1	9/2017	Mosher et al.

FOREIGN PATENT DOCUMENTS

WO	WO-9814196	A1	4/1998
WO	WO-9930690	A1	6/1999
WO	WO-1999030690		6/1999
WO	WO-0145667	A2	6/2001
WO	WO-02089775	A1	11/2002
WO	WO-2007070843	A2	6/2007
WO	WO-2009116078	A2	9/2009
WO	WO-2011031462	A2	3/2011
WO	WO-2011128783	A2	10/2011
WO	WO-2012085249	A2	6/2012
WO	WO-2014055667	A1	4/2014
WO	WO-2014178065	A1	11/2014
WO	WO-2017161339	A1	9/2017

OTHER PUBLICATIONS

Parish, "How do salt and sugar prevent microbial spoilage?", Scientific American, 2006 <https://www.scientificamerican.com/article/how-do-salt-and-sugar-pre/> (Year: 2006).*

AAPS American Association of Pharmaceutical Scientists, Preliminary Program, 2011 AAPS Annual Meeting and Exposition, Washington, D.C., Oct. 23-27, 2011, 112 pages.

Ahlin et al. Investigation of polymeric nanoparticles as carriers of enalaprilat for oral administration. *Int'l. J. Pharmaceutics* 239:113-120 (2002).

Allen et al. Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids. *Am. J. Health-Syst. Pharm.* 55:1915-1920 (1998).

Allen. Lisinopril 1 mg/mL oral liquid US Pharm. 38(2):36-37 (2013).

Al-Omari et al. Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations. *Journal of Pharmaceutical and Biomedical Analysis* 25:893-902 (2001).

Bhardwaj et al. Study of forced degradation behavior of enalapril maleate by LC and LC-MS and development of a validated stability-indicating assay method. *Journal of Pharmaceutical and Biomedical Analysis* 46:113-120 (2008).

Blowey. Update on the pharmacologic treatment of hypertension in pediatrics. *Journal of Clinical Hypertension* 14(6), 383-387 (2012).

Boukarim et al. Preservatives in liquid pharmaceutical preparations. *The Journal of Applied Research* 9(1 & 2):14-17 (2009).

Bourgault et al., Reference-based pricing of prescription drugs: exploring the equivalence of angiotensin-converting-enzyme inhibitors. *CMAJ* 161:255-60 (1999).

Brilla et al., Lisinopril-Mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 102:1388-1393 (2000).

Cabot Corporation, "Influence of CAB-O-SIL® M-5P on the Angle of Repose and Flow Rates of Pharmaceutical Powders," 10 pages (2004).

Calabro et al. Hemodynamic effects of a single oral dose of enalapril among children with asymptomatic chronic mitral regurgitation. *American Heart Journal* 138(5, Pt. 1):955-961 (1999).

Definition of Hypertension (1 page) retrieved from: <http://medical-dictionary.thefreedictionary.com/hypertension> (2008).

Delucchi et al., "Enalapril and prednisone in children with nephrotic-range proteinuria," *Pediatric nephrology* (Berlin, Germany) (2000), 14(12), 1088-91, Database: Medline.

Drug Information on Enalapril (3 pages), 2001. retrieved from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/18-998s058_Vasotec.cfm.

drugs.com. Enalapril Tablets Soluble. Website [online]. [available online May 9, 2010] [retrieved on Jan. 16, 2014], 11 pages.

Retrieved from the Internet< URL: <https://web.archive.org/web/20100509220009/http://www.drugs.com/pro/enalapril-tablets-soluble.html>>. Enalapril Tablets Soluble-Clinical Pharmacology; Indications and Usage for Enalapril Tablets Soluble; Enalapril Tablets Soluble Dosage and Administration.

Glass et al. Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. *J. Pharm. Sci.* 9(3):398-426 (2006).

Gulf Cooperation Council. The GCC Guidelines for Stability Testing of Drug Substances and Pharmaceutical Products. Publication [online]. Edition Two, 1428 H-2007 G [available online Jul. 2011] [retrieved on Feb. 3, 2014]. Retrieved from the Internet< URL: https://web.archive.org/web/20110726040053/http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisation/GCC/T_opics_under_Harmonisation/Stability.pdf>. p. 22, 2.9.3; p. 25, 2.9.7.

Handbook of Pharmaceutical Excipients, Fifth edition, edited by Raymond C. Rowe et al., London: Pharmaceutical Press, 2006, (monographs for citric acid monohydrate, sodium benzoate, sodium citrate, sodium hydroxide, and xylitol), 23 pages.

Harris, Daniel C. Exploring Chemical Analysis, 4th edition. New York:W.H. Freeman and Company, 2009 (Chapters 8,9,21 and 22), 105 pages.

Hensel et al. Transesterification reactions off parabens (Alkyl 4-Hydroxybenzoates) with polyols in aqueous solution. *J. Pharm. Sci.* 84(1):115-119 (1995).

Hsu et al. Enalapril in Infants With Single Ventricle: Results of a Multicenter Randomized Trial. *Circulation* 122(4):333-340 (2010).

US 10,786,482 B2

Page 3

(56)

References Cited

OTHER PUBLICATIONS

- Hsu et al. Rationale and design of a trial of angiotensin-converting enzyme inhibition in infants with single ventricle. *American Heart Journal* 157(1):37-45 (2009).
- Kalaitzidis et al. Prehypertension: is it relevant for nephrologists? *Kidney International* 77:194-200 (2010).
- Li et al. Lessons learned from a pediatric clinical trial: The Pediatric Heart Network Angiotensin-Converting Enzyme Inhibition in Mitral Regurgitation Study. *American Heart Journal* 161(2):233-240 (2011).
- Lima et al., "Stability and in vitro release profile of enalapril maleate from different commercially available tablets: Possible therapeutic implications," *Journ. Pharmac. and Biomed. Analysis*, 47, pp. 934-937 (2008).
- Lipshultz, "Exposure to anthracyclines during childhood causes cardiac injury," *Seminars in Oncology* (2006), 33(3, Suppl. 8), S8-S14., Database: CAPLUS, DOI:10.1053/j.seminoncol.2006.04.019.
- Ma et al., HPLC and LC-MS studies of the transesterification reaction of Methylparaben with twelve 3- to 6-carbon sugar alcohols and propylene glycol and the isomerization of the reaction products by acyl migration. *Journal of Chromatographic Science*, 40(3):170-177, 2002.
- Meyers et al. Pharmacotherapy Review of Chronic Pediatric Hypertension. *Clinical Therapeutics* (2011), 33(10), 1331-1356. Database: CAPLUS, DOI:10.1016/j.clinthera.2011.09.003.
- Miller et al., "Enalapril: a well-tolerated and efficacious agent for the paediatric hypertensive patient," *Journal of hypertension. Supplement : official journal of the International Society of Hypertension* (1986), 4(5), S413-6, Database: Medline.
- Mir et al., "Effect of carvedilol on QT duration in pediatric patients with congestive heart failure," *Clinical Drug Investigation* (2004), 24(1), 9-15. Database: CAPLUS, DOI:10.2165/00044011-200424010-00002.
- Momma, "ACE inhibitors in pediatric patients with heart failure," *Paediatric drugs* (2006), 8(1), 55-69, Database: Medline.
- Nahata et al. Stability of enalapril maleate in three extemporaneously prepared oral liquids. *Am. J. Health-Syst Pharm* 55:1155-1157 (1998).
- Nakamura et al., "The kinetic profiles of enalapril and enalaprilat and their possible developmental changes in pediatric patients with congestive heart failure," *Clinical pharmacology and therapeutics* (1994), 56(2), 160-8, Database: Medline.
- National institutes of Health. 'MedlinePlus: Hypertension'. Website [online]. [available online May 20, 2012] [retrieved on Jan. 16, 2014], 5 pages. Retrieved from the Internet<URL:https://web.archive.org/web/20120520035026/http://www.nlm.nih.gov/medlineplus/ency/article/000468.htm>.
- Nationwide Children's Hospital. 'Enalapril Oral Suspension' Publication [online]. Mar. 29, 2010 [retrieved on Jan. 14, 2014], 1 page. Retrieved from the Internet<URL:http://www.nationwidechildrens.org/Document/Get/78785>.
- Niazi, Sarfaraz K. *Handbook of Pharmaceutical Manufacturing Formulations: Liquid Products*, vol. 3, Second edition. New York: Informa Healthcare USA, Inc., 2009, 400 pages.
- Nicolosi et al., The prognostic value of predischARGE quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 trial. *European Heart Journal*, 17:1646-1656, 1996.
- Novartis AG (Appellants) v. Torrent Pharmaceuticals Limited, Apotex Inc., Mylan Pharmaceuticals Inc.*, (Appellees), No. 2016-1352, Slip Opinion decided Apr. 12, 2017, 27 pages.
- Nunn et al. Formulation of medicines for children. *British Journal of Clinical Pharmacology*, 59:6, pp. 674-676 (2005).
- Packer et al., Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation*, 100:2312-1218, 1999.
- Patel et al., "Extemporaneous Dosage Form for Oral Liquids," *Pharmacophore*, vol. 2, No. 2, pp. 86-103 (2011).
- PCT Patent Application No. PCT/US2016/059348 International Search Report and Written Opinion dated Jan. 3, 2017.
- PCT Patent Application No. PCT/US2017/023074 International Search Report and Written Opinion dated Jun. 16, 2017.
- Product Information of Bicitra, "Sodium Citrate and Citric Acid Oral Solution USP." 2 pages.
- Product Information of Ora-Sweet(1 page, 2013) retrieved from, <http://www.stobec.com/documents/data/8196.pdf>.
- Proesmans et al., "Enalapril in children with Alport syndrome," *Pediatric nephrology* (Berlin, Germany) (2004), 19(3), 271-5, Database: Medline.
- Proesmans et al., Long-term therapy with enalapril in patients with nephrotic-range proteinuriam, *Pediatric nephrology* (Berlin, Germany) (1996), 10(5), 587-9, Database: Medline.
- Proesmans et al., "Enalapril in pediatric patients with Alport syndrome: 2 years' experience," *European Journal of Pediatrics* (2000), 159(6), 430-433. Database: CAPLUS, DOI:10.1007/s004310051301.
- Raia, et al., Angiotensin-converting enzyme inhibitors: A Comparative review. *DPIC, The Annals of Pharmacotherapy*, 24:506-525, 1990.
- Ramusovic et al., "Determination of enalapril and enalaprilat in small human serum quantities for pediatric trials by HPLC-tandem mass spectrometry," *Biomedical Chromatography* (2012), 26(6), 697-702. Database: CAPLUS, DOI:10.1002/bmc.1716.
- Rezende et al., "Stability and Compatibility Study on Enalapril Maleate Using Thermoanalytical Techniques," *Journ Thermal Analysis and Calorimetry*, 93:3, pp. 881-886 (2008).
- Rose et al., Stability of Lisinopril syrup (2 mg/mL) extemporaneously compounded from tablets. *Int J Pharm Compd*. 4(5):398-399 (2000).
- Russell, Craig Allen, *Paediatric Drug Development:— Reformulation, In Vitro, Genomic and In Vivo Evaluation*. Thesis, Apr. 2014, 330 pages.
- Schlatter et al., Stability of Enalapril solutions prepared from tablets in sterile water. *Australian J. Hospital Pharmacy*, 27:395, 1997.
- Seikaly. Hypertension in children: an update on treatment strategies. *Current Opinion in Pediatrics*, 19:170-177, 2007.
- Silber et al., "Design and baseline characteristics for the ACE inhibitor after anthracycline (AAA) study of cardiac dysfunction in long-term pediatric cancer survivors," *American Heart Journal* (2001), 142(4), 577-585. Database: CAPLUS, DOI:10.1067/mhj.2001.118115.
- Silber et al., "Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines," *Journal of Clinical Oncology* (2004), 22(5), 820-828. Database: CAPLUS, DOI:10.1200/JCO.2004.06.022.
- Simončič et al., "Use of microcalorimetry in determination of stability of enalapril maleate and enalapril maleate table formulations," *Int'l. Journ. Pharmaceutics*, 342, pp. 145-151 (2007).
- Sipahi et al. Effect of Antihypertensive Therapy on Incident Stroke in Cohorts with Prehypertensive Blood Pressure Levels: A Meta-Analysis of Randomized Controlled Trials, *Stroke: Journal of the American Heart Association* [online], Dec. 8, 2011 (retrieved Jan. 16, 2014). 10 pages. Retrieved from the Internet<URL:http://www.medpagetoday.com/upload/2011/12/9/Stroke-2011-Sipahi-STROKEAHA.111.636829.pdf>.
- Sipahi et al., Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis, *J. Am. Coll. Cardiol*. 48, 833-838, 2006.
- Garrett. Prediction of stability of drugs and pharmaceutical preparations. *Journal of Pharmaceutical Sciences* 51(9):811-833 (1962).
- Standing et al. Paediatric formulations-Getting to the heart of the problem. *International Journal of Pharmaceutics* (2005), 300(1-2), 56-66. Database: CAPLUS.
- Stanisz, "Evaluation of stability of enalapril maleate in solid phase," *Journ. Pharma. and Biomed. Analysis*, 31, pp. 375-380 (2003).
- Teva UK, Limited. Enalapril Maleate 2.5 mg, 5 mg, 10 mg and 20 mg Tablets. Product Brochure [online]. Mar. 2011 [retrieved on Jan. 14, 2014], 8 pages. Retrieved from the Internet:<URL:http://www.drugs.com/uk/pdf/leaflet/213793.pdf>. col. 2, lines 70-76.
- Thompson et al., Characterization of an extemporaneous liquid formulation of lisinopril. *Am J Health Syst Pharm*. 60(1):69-74 (2003).

US 10,786,482 B2

Page 4

(56)

References Cited

OTHER PUBLICATIONS

Tian et al., Effect of organic anion-transporting polypeptide IB1 (OATP1B1) polymorphism on the single- and multiple-dose pharmacokinetics of enalapril in healthy Chinese adult men *Clinical Therapeutics*, 33(5): 655 (2011).

U.S. Appl. No. 13/670,355 Office Action dated Feb. 8, 2013.

U.S. Appl. No. 13/670,355 Office Action dated Jul. 30, 2013.

U.S. Appl. No. 13/914,452 Office Action dated Aug. 28, 2013.

U.S. Appl. No. 14/433,502 Office Action dated Dec. 29, 2016.

U.S. Appl. No. 14/433,502 Restriction Requirement dated Apr. 12, 2016.

U.S. Appl. No. 14/934,752 First Action Interview dated Jan. 25, 2016.

U.S. Appl. No. 14/934,752 Office Action dated Apr. 26, 2016.

U.S. Appl. No. 15/081,603 First Action Interview dated Sep. 2, 2016.

U.S. Appl. No. 15/081,603 First Action Interview Office Action Summary dated Jan. 17, 2017.

U.S. Appl. No. 15/268,095 Office Action dated Oct. 13, 2016.

U.S. Appl. No. 15/433,743 Office Action dated Jun. 5, 2017.

U.S. Appl. No. 15/613,622 Office Action dated Aug. 11, 2017.

U.S. Appl. No. 15/850,732 Office Action dated Mar. 1, 2018.

U.S. Appl. No. 16/003,994 Office Action dated Sep. 20, 2018.

U.S. Appl. No. 15/802,341 Office Action dated Apr. 19, 2018.

Van Hecken et al. Absence of a pharmacokinetic interaction between enalapril and frusemide *British Journal of Clinical Pharmacology*, 1987, vol. 23:84-87.

Vasotec (Enalapril Maleate) Product Insert (2010) 5 pages (Best copy available).

Wang et al., "Eudragit E Accelerated the Diketopiperazine Formation of Enalapril Maleate Determined by Thermal FTIR Microspectroscopic Technique," *Pharmaceutical Research*, vol. 21, No. 11, Nov. 2004.

Webster et al., The Stability of Lisinopril as an extemporaneous syrup. *Int J Pharm Compd.* 1(5):352-353 (1997).

Wells et al., "A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension," *Journal of Clinical Pharmacology* (2002), 42(8), 870-880. Database: CAPLUS, DOI:10.1177/009127002401102786.

Wells et al., "The Pharmacokinetics of Enalapril in Children and Infants with Hypertension," *J. Clin Pharmacol* 41:1064-1074 (2001).

Williams et al., "Factors affecting growth in infants with single ventricle physiology: a report from the Pediatric Heart Network

Infant Single Ventricle Trial," *The Journal of Pediatrics* (2011), 159(6), 1017-22.e2, Database: Medline.

Parish: How do salt and sugar prevent microbial spoilage?; *Scientific American* (2006).

Sosnowska et al.: Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared From Commercially Available Tablets; *Acta Poloniae Pharmaceutica—Drug Research*; vol. 66, No. 3; pp. 321-326 (2009).

U.S. Appl. No. 15/483,691 Office Action dated Jun. 8, 2017.

U.S. Appl. No. 16/242,898 Office Action dated May 2, 2019.

Al-Omari, M.M. et al., Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations, *J. of Pharmaceutical and Biomedical Analysis* 25 (2001) 893-902.

Casas, Marta et al., Physicochemical stability of captopril and enalapril extemporaneous formulations for pediatric patients, *Pharm Dev Technol*, 2015; 20(3): 271-278.

European Search Report for EP17767676.4 dated Oct. 8, 2019.

Extended European Search Report dated Feb. 19, 2016, for EP Application No. 13844343.7.

Final Office Action dated Nov. 19, 2019 for U.S. Appl. No. 16/242,898.

International Search Report and Written Opinion dated Jun. 16, 2017 for PCT/US17/023074 (WO2017161339).

MC Nahata et al., Stability of enalapril maleate in three extemporaneously prepared oral liquids, *American Journal of Health System Pharmacy*, American Society of Healthy Systems Pharmacy, US, vol. 55, No. 11, Jun. 1, 1998, pp. 1155-1157.

Nationwide Children's Hospital Pharmacy, Columbus, Ohio, Enalapril Oral Suspension Dosage Form, Mar. 29, 2010, XP055291016.

PCT/US2013/63096 International Preliminary Report on Patentability dated Apr. 7, 2015.

PCT/US2013/63096 International Search Report and Written Opinion dated Feb. 20, 2014.

Ripley et al., "Pharmacokinetic Assessment of an Oral Enalapril Suspension for Use in Children," *Biopharmaceutics & Drug Disposition* 21:339-344 (2000).

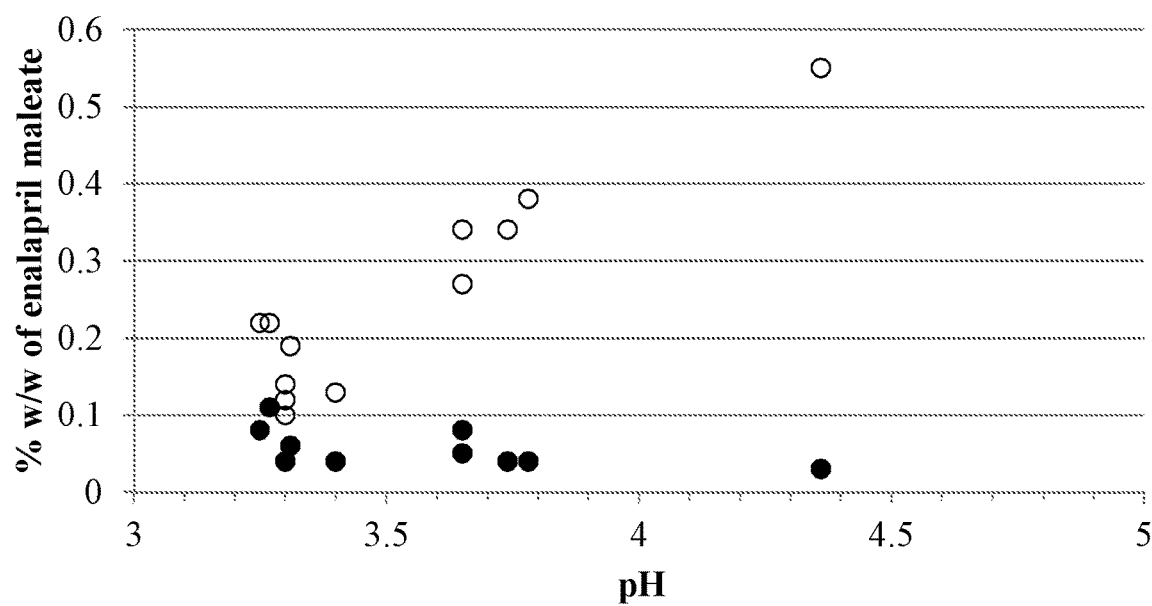
Sandoz, Limited. Amoxicillin 125 mg/5 ml Powder for Oral Suspension. Product brochure [online]. Jul. 2012 [retrieved on Jan. 17, 2014]. Retrieved from the Internet <URL:http://www.drugs.com/uk/pdf/leaflet/196044.pdf >.

Silvergate Pharmaceuticals, Inc. (Plaintiff) v. Bionpharma, Inc. (Defendant) C.A. No. 1:16-cv-00876-SLR (consolidated). Bionpharma Inc.'s Invalidity Contentions Pursuant to Delaware Default Standard Rule 4(d). Jun. 9, 2017, 50 pages.

* cited by examiner

FIG. 1

● Enalapril diketopiperazine; ○ Enalaprilat



U.S. Patent

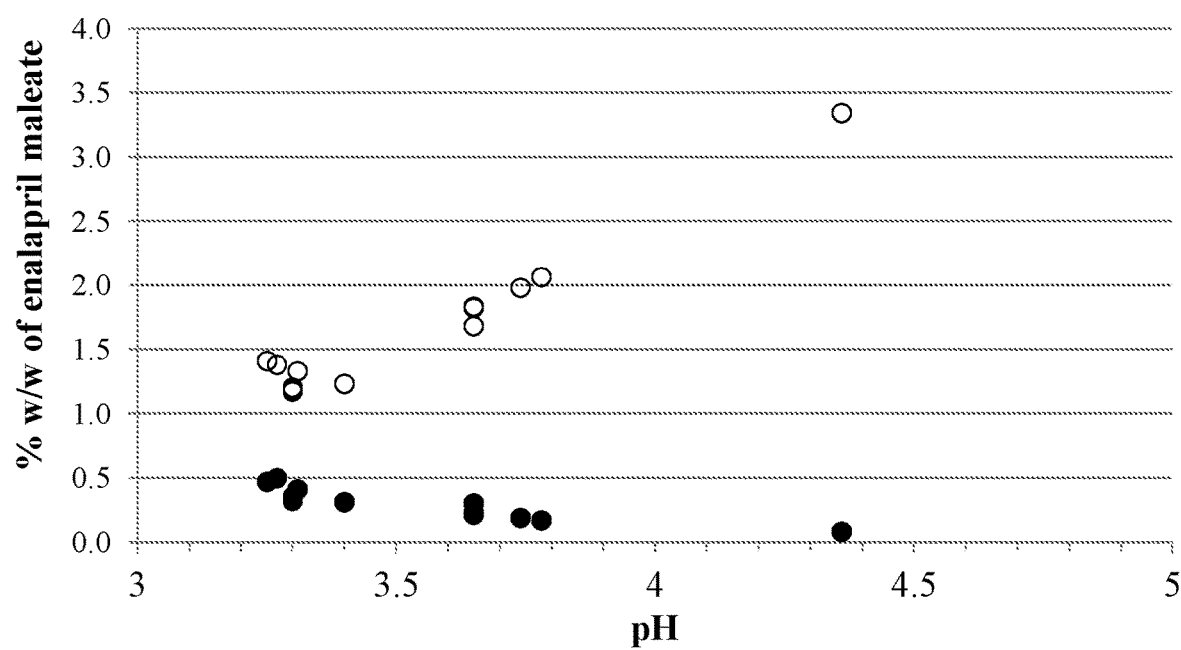
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FIG. 2

● Enalapril diketopiperazine; ○ Enalaprilat



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ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

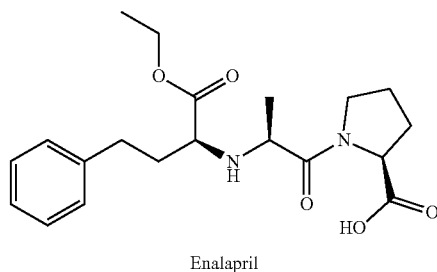
This application is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018, which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

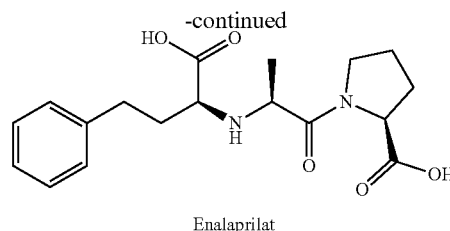
Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



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Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5 \pm 3^\circ \text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5 \pm 3^\circ \text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water;

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wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an

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adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/mL enalapril maleate; (ii) about 0.7 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 mg/mL of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed descrip-

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tion that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treat-

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ment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83

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mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodi-

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ments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatococin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005-maltodextrin, sorbitol, and fructose combination and Product Code 918.010-water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), Maltisweet™ (maltitol solution, Ingredient), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn

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syrup, Ingredient), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155

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mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32

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mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5%

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w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2%

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w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and Preservative Incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

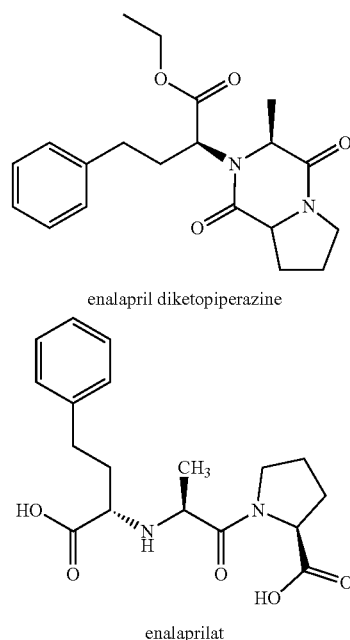
In some embodiments, the oral liquid formulation comprises a buffer.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:

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In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml,

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about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/mL, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1 mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34%

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w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1% w/w to about 5% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5% w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/mL, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the

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oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1% w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise,

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cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent.

Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18

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months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is $5\pm 3^\circ\text{C}$. In some embodiments, refrigerated condition is about 2°C ., about 2.1°C ., about 2.2°C ., about 2.3°C ., about 2.4°C ., about 2.5°C ., about 2.6°C ., about 2.7°C ., about 2.8°C ., about 2.9°C ., about 3°C ., about 3.1°C ., about 3.2°C ., about 3.3°C ., about 3.4°C ., about 3.5°C ., about 3.6°C ., about 3.7°C ., about 3.8°C ., about 3.9°C ., about 4°C ., about 4.1°C ., about 4.2°C ., about 4.3°C ., about 4.4°C ., about 4.5°C ., about 4.6°C ., about 4.7°C ., about 4.8°C ., about 4.9°C ., about 5°C ., about 5.1°C ., about 5.2°C ., about 5.3°C ., about 5.4°C ., about 5.5°C ., about 5.6°C ., about 5.7°C ., about 5.8°C ., about 5.9°C ., about 6°C ., about 6.1°C ., about 6.2°C ., about 6.3°C ., about 6.4°C ., about 6.5°C ., about 6.6°C ., about 6.7°C ., about 6.8°C ., about 6.9°C ., about 7°C ., about 7.1°C ., about 7.2°C ., about 7.3°C ., about 7.4°C ., about 7.5°C ., about 7.6°C ., about 7.7°C ., about 7.8°C ., about 7.9°C ., or about 8°C . At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. $25\pm 5^\circ\text{C}$.; $55\pm 10\%$ RH). In some instances, an accelerated condition is at about 25°C ., about 30°C ., about 35°C ., about 40°C ., about 45°C ., about 50°C ., about 55°C ., or about 60°C . In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40°C ., or 60°C ., at ambient humidity. In yet further instances, an accelerated condition is about 40°C ., at $75\pm 5\%$ RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about

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15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and

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the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for an enalapril oral liquid formulation. In other

embodiments, a syrup is used for as a vehicle for an enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for an enalapril oral liquid formulation. Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate. In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and

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mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of an enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to an enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof, and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the

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liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2x10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

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Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset

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of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of

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about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76 mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet

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formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does not improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to

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a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxyben-

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zamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltiazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartan, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

“Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

“Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms

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“patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or

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undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at 60° C.	Formulation					
	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

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Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29

TABLE B-1-continued

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

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TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours	Formulation		
at 60° C.	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		

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TABLE C-1-continued

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)								
25		Storage		Formulation				
		° C.	Weeks	C1	C2	C3	C4	C5
Liquid Formulations								
30	Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
			4	0.02	0.03	0.03	0.03	0.02
		19-23	8	0.03	0.04	0.04		
			0	0.03	0.04	0.04	0.02	0.02
	4		0.05	0.09	0.11	0.05	0.04	
	8		0.08	0.17	0.19			
	35	40	0	0.03	0.04	0.04	0.02	0.02
			4	0.35	0.91	1.10	0.31	0.21
Enalaprilat		5	8	0.65	1.80	2.05		
			0	0.18	0.14	0.12	0.13	0.19
	4		0.18	0.15	0.12	0.43	0.53	
	8		0.55	0.38	0.34			
	19-23	0	0.18	0.14	0.12	0.13	0.19	
		4	1.35	0.83	0.80	1.75	2.29	
		8	3.34	2.06	1.98			
		0	0.18	0.14	0.12	0.13	0.19	
40	40	4	10.49	6.08	6.11	12.30	16.14	
		8	24.37	14.12	14.22			

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

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TABLE D-1

Composition of Enalapril Maleate Formulations						
Component	D1	D2	D3	D4	D5	D6
Powder Formulation (grams)						
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)									
		Storage		Formulation					
		° C.	Weeks	D1	D2	D3	D4	D5	D6
Liquid Formulations									
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04	
		4	0.07	0.03	0.05	0.05	0.03		
		8	0.11	0.06	0.08	0.08	0.05		
		12	0.08	0.04	0.06	0.06			
		26	0.11	0.07	0.09	0.07			
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04	
		4	0.27	0.21	0.24	0.16	0.12	0.12	
		8	0.50	0.41	0.47	0.30	0.21	0.22	
		12	0.62	0.52	0.58	0.35			
		26	1.39	1.20	1.33	0.76			
	40	0	0.04	0.02	0.03	0.03	0.04	0.04	
		4	2.87	2.32	2.73	1.57	1.21	1.13	
		8	5.13	4.42	5.44	2.97	2.23	2.16	
		12	6.86	5.90	6.90	3.91			
		26	13.63	12.18	13.56	7.74			
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14	
		4	0.15	0.12	0.06	0.17	0.13		
		8	0.22	0.19	0.22	0.27	0.34		
		12	0.20	0.17	0.19	0.22			
		8	0.32	0.30	0.30	0.39			
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14	
		4	0.69	0.66	0.69	0.86	0.74	0.76	
		8	1.38	1.33	1.41	1.68	1.83	1.82	
		12	1.71	1.68	1.73	2.15			
		26	3.63	3.61	3.59	4.55			

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TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Storage		Formulation					
° C.	Weeks	D1	D2	D3	D4	D5	D6
40	0	0.03	0.02	0.03	0.03	0.13	0.14
	4	4.76	4.42	4.76	6.45	5.55	5.24
	8	8.95	8.64	9.61	12.94	12.73	12.18
	12	11.01	10.64	11.41	16.16		
	26	17.18	17.11	18.30	27.36		

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Example E: Stability of Solution Formulations of
Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C. \pm 3° C., at room temperature (19-23° C.) and at 40° C. \pm 2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		

-continued

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	° C.	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
	19-23	62	0.18	0.18	0.16	0.14		
		0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28
		12	0.58	0.59	0.53	0.51	0.48	0.45
		26	1.10	1.10	1.00	0.95	0.97	0.92
		52					2.30	2.15
	40	62	3.02	3.04	2.75	2.64		
		0	0.01	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76	1.68
		8	4.02	3.99	3.99	3.62	3.37	3.13
		12	6.72	6.42	6.47	6.00	5.53	5.29
		26	11.01	10.64	11.41	16.16		
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
	19-23	62	0.75	0.75	0.74	0.71		
		0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.65	0.65	0.68	0.70	0.50	0.46
		8	1.17	1.19	1.20	1.23	1.03	0.95
		12	1.67	1.69	1.72	1.80	1.30	1.21
		26	3.36	3.38	3.42	3.57	3.07	2.90
	40	52					6.32	5.88
		62	7.99	8.02	8.04	8.57		

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TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Storage		Formulation					
° C.	Weeks	E1	E2	E3	E4	E5	E6
40	0	0.00	0.00	0.01	0.02	0.00	0.00
	4	4.85	4.93	5.19	5.42	3.33	3.25
	8	8.08	8.06	8.56	9.01	6.65	6.35
	12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. 1 (5° C. ±3° C.) and FIG. 2 (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution Vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5),

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to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirman’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_m were approximately 115% and

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109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. An oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
 - (iii) about 1 mg/ml sodium benzoate; and
 - (iv) water;
 wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5\pm 3^\circ\text{C}$.
2. The oral liquid formulation of claim 1 further comprising a sweetener.
3. The oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. The oral liquid formulation of claim 1 further comprising a flavoring agent.
5. The oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
6. The oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
7. The oral liquid formulation of claim 1, wherein the buffer comprises about 0.8 to about 3.5 mg/ml citric acid.
8. The oral liquid formulation of claim 1, wherein the buffer comprises about 0.1 to about 0.8 mg/ml sodium citrate.
9. The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is less than about 3.5.
10. The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.
11. The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is about 3.3.
12. The oral liquid formulation of claim 1, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about $5\pm 3^\circ\text{C}$.
13. An oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

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(ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;

(iii) about 1 mg/ml sodium benzoate;

(iv) water; and

(v) optionally a sweetener, a flavoring agent, or both;

wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5\pm 3^\circ\text{C}$.

14. An oral liquid formulation, comprising:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;

(iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens; and

(iv) water;

wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5\pm 3^\circ\text{C}$.

15. The oral liquid formulation of claim 14 further comprising a sweetener.

16. The oral liquid formulation of claim 15, wherein the sweetener is sucralose.

17. The oral liquid formulation of claim 14 further comprising a flavoring agent.

18. The oral liquid formulation of claim 14, wherein the formulation does not contain mannitol.

19. The oral liquid formulation of claim 14, wherein the formulation does not contain silicon dioxide.

20. The oral liquid formulation of claim 14, wherein the pH of the oral liquid formulation is less than about 3.5.

21. The oral liquid formulation of claim 14, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.

22. The oral liquid formulation of claim 14, wherein the pH of the oral liquid formulation is about 3.3.

23. The oral liquid formulation of claim 14, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about $5\pm 3^\circ\text{C}$.

24. The oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.

25. The oral liquid formulation of claim 1, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

26. The oral liquid formulation of claim 1, wherein the buffer is present at a concentration of about 10 mM in the oral liquid formulation.

27. The oral liquid formulation of claim 14, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.

28. The oral liquid formulation of claim 14, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

* * * * *



US010918621B2

(12) **United States Patent**
Mosher et al.

(10) **Patent No.:** **US 10,918,621 B2**

(45) **Date of Patent:** ***Feb. 16, 2021**

(54) **ENALAPRIL FORMULATIONS**

(71) Applicant: **Silvergate Pharmaceuticals, Inc.**,
Greenwood Village, CO (US)

(72) Inventors: **Gerold L. Mosher**, Kansas City, MO
(US); **David W. Miles**, Kansas City,
MO (US)

(73) Assignee: **SILVERGATE**
PHARMACEUTICALS, INC.,
Greenwood Village, CO (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **16/991,575**

(22) Filed: **Aug. 12, 2020**

(65) **Prior Publication Data**

US 2020/0368200 A1 Nov. 26, 2020

Related U.S. Application Data

(63) Continuation of application No. 16/883,553, filed on
May 26, 2020, now Pat. No. 10,799,476, which is a
continuation of application No. 16/242,898, filed on
Jan. 8, 2019, now Pat. No. 10,772,868, which is a
continuation of application No. 16/177,159, filed on
Oct. 31, 2018, now Pat. No. 10,786,482, which is a
continuation of application No. 16/003,994, filed on
(Continued)

(51) **Int. Cl.**

A61K 31/401 (2006.01)
A61K 9/00 (2006.01)
A61K 47/26 (2006.01)
A61K 47/12 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 31/401** (2013.01); **A61K 9/0053**
(2013.01); **A61K 9/0095** (2013.01); **A61K**
47/12 (2013.01); **A61K 47/26** (2013.01)

(58) **Field of Classification Search**

CPC **A61K 31/401**; **A61K 47/12**; **A61K 47/26**;
A61K 9/0053; **A61K 9/0095**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,374,829 A 2/1983 Harris et al.
4,472,380 A 9/1984 Harris et al.
(Continued)

FOREIGN PATENT DOCUMENTS

CA 1275350 C 10/1990
EP 2903690 A1 8/2015
(Continued)

OTHER PUBLICATIONS

AAPS American Association of Pharmaceutical Scientists, Prelimi-
nary Program, 2011 AAPS Annual Meeting and Exposition, Wash-
ington, D.C., Oct. 23-27, 2011, 112 pages.

(Continued)

Primary Examiner — Savitha M Rao

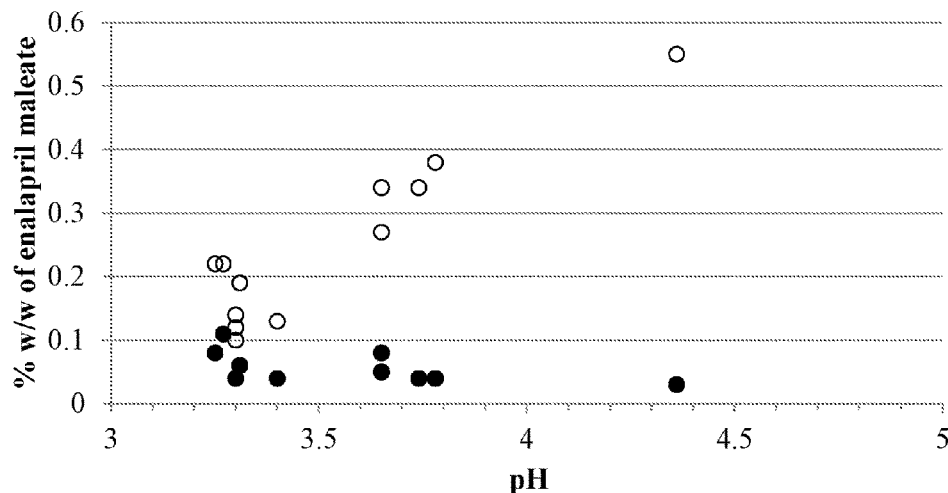
(74) *Attorney, Agent, or Firm* — Wilson Sonsini Goodrich
& Rosati, P C.

(57) **ABSTRACT**

Provided herein are stable enalapril oral liquid formulations.
Also provided herein are methods of using enalapril oral
liquid formulations for the treatment of certain diseases
including hypertension, heart failure and asymptomatic left
ventricular dysfunction.

30 Claims, 2 Drawing Sheets

● Enalapril diketopiperazine; ○ Enalaprilat



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Related U.S. Application Data

Jun. 8, 2018, now Pat. No. 10,154,987, which is a continuation of application No. 15/802,341, filed on Nov. 2, 2017, now Pat. No. 10,039,745, which is a continuation of application No. 15/613,622, filed on Jun. 5, 2017, now Pat. No. 9,808,442, which is a continuation of application No. 15/081,603, filed on Mar. 25, 2016, now Pat. No. 9,669,008.

(60) Provisional application No. 62/310,198, filed on Mar. 18, 2016.

(56) References Cited

U.S. PATENT DOCUMENTS

4,510,083	A	4/1985	Blacklock et al.
4,743,450	A	5/1988	Harris et al.
4,793,998	A	12/1988	Murthy et al.
4,830,853	A	5/1989	Murthy et al.
4,931,430	A	6/1990	Sudilovsky et al.
5,049,553	A	9/1991	Sudilovsky
5,698,562	A	12/1997	Mendes et al.
6,028,222	A	2/2000	Dietlin et al.
6,300,361	B1	10/2001	Vivilecchia et al.
6,300,362	B1	10/2001	Vivilecchia et al.
6,413,988	B1	7/2002	De Proost
6,509,350	B2	1/2003	Vivilecchia et al.
6,790,861	B2	9/2004	Vivilecchia et al.
6,869,963	B2	3/2005	Patel et al.
6,977,257	B2	12/2005	Parab et al.
7,101,888	B2	9/2006	Reo et al.
7,605,148	B2	10/2009	Batta et al.
8,153,824	B2	4/2012	Sesha
8,568,747	B1	10/2013	Rajewski et al.
8,778,366	B2	7/2014	Rajewski et al.
8,927,028	B2	1/2015	Grenier et al.
9,463,183	B1	10/2016	Mosher et al.
9,616,096	B1	4/2017	Mosher et al.
9,669,008	B1	6/2017	Mosher et al.
9,808,442	B2	11/2017	Mosher
9,855,214	B2	1/2018	Rajewski
9,968,553	B1	5/2018	Rajewski
1,003,974	A1	8/2018	Mosher; Gerold L
1,015,498	A1	12/2018	Mosher; Gerold L et al.
2004/0171669	A1	9/2004	Chenevier
2004/0258757	A1	12/2004	Bosch et al.
2006/0094760	A1	5/2006	Fawzy et al.
2006/0121066	A1	6/2006	Jaeger et al.
2007/0265344	A1	11/2007	Strobel et al.
2008/0221156	A1	9/2008	Spireas
2008/0234291	A1	9/2008	Francois et al.
2009/0269287	A1	10/2009	Berta
2010/0222334	A1	9/2010	Talamonti et al.
2011/0003798	A1	1/2011	Okram et al.
2014/0100260	A1	4/2014	Rajewski et al.
2015/0148335	A1	5/2015	Bova et al.
2015/0258027	A1	9/2015	Rajewski
2017/0119840	A1	5/2017	Mosher et al.
2017/0209523	A1	7/2017	Mosher et al.
2017/0266159	A1	9/2017	Mosher et al.
2018/0055821	A1	3/2018	Mosher et al.
2019/0070147	A1	3/2019	Mosher et al.

FOREIGN PATENT DOCUMENTS

WO	WO-9814196	A1	4/1998
WO	WO-9930690	A1	6/1999
WO	WO-1999030690		6/1999
WO	WO-0145667	A2	6/2001
WO	WO-02089775	A1	11/2002
WO	WO-2007070843	A2	6/2007
WO	WO-2009116078	A2	9/2009
WO	WO-2011031462	A2	3/2011
WO	WO-2011128783	A2	10/2011
WO	WO-2012085249	A2	6/2012

WO	WO-2014055667	A1	4/2014
WO	WO-2014178065	A1	11/2014
WO	WO-2017075368	A1	5/2017
WO	WO-2017161339	A1	9/2017

OTHER PUBLICATIONS

Ahlin et al. Investigation of polymeric nanoparticles as carriers of enalaprilat for oral administration. *Int'l. J. Pharmaceutics* 239:113-120 (2002).

Allen et al. Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids. *Am J. Health-Syst Pharm* 55:1915-1920 (1998).

Allen. Lisinopril 1 mg/mL oral liquid US Pharm. 38(2):36-37 (2013).

Al-Omari et al. Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations. *Journal of Pharmaceutical and Biomedical Analysis* 25:893-902 (2001).

Al-Omari, M.M. et al., Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations, *J. of Pharmaceutical and Biomedical Analysis* 25 (2001) 893-902.

Bhardwaj et al. Study of forced degradation behavior of enalapril maleate by LC and LC-MS and development of a validated stability-indicating assay method. *Journal of Pharmaceutical and Biomedical Analysis* 46:113-120 (2008).

Blowey. Update on the pharmacologic treatment of hypertension in pediatrics. *Journal of Clinical Hypertension* 14(6), 383-387 (2012).

Boukarim et al. Preservatives in liquid pharmaceutical preparations. *The Journal of Applied Research* 9(1 & 2):14-17 (2009).

Bourgault et al., Reference-based pricing of prescription drugs: exploring the equivalence of angiotensin-converting-enzyme inhibitors. *CMAJ* 161:255-60 (1999).

Brilla et al., Lisinopril-Mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 102:1388-1393 (2000).

Cabot Corporation, "Influence of CAB-O-SIL® M-5P on the Angle of Repose and Flow Rates of Pharmaceutical Powders," 10 pages (2004).

Calabro et al. Hemodynamic effects of a single oral dose of enalapril among children with asymptomatic chronic mitral regurgitation. *American Heart Journal* 138(5, Pt. 1):955-961 (1999).

Casas, M., et al., "Physicochemical Stability of Captopril and Enalapril Extemporaneous Formulations for Pediatric Patients," *Pharmaceutical Development and Technology*, 20(3):271-278 (May 2015).

Definition of Hypertension (1 page) retrieved from: <http://medical-dictionary.thefreedictionary.com/hypertension> (2008).

Delucchi et al., "Enalapril and prednisone in children with nephrotic-range proteinuria," *Pediatric nephrology* (Berlin, Germany) (2000), 14(12), 1088-91, Database: MEDLINE.

Drug Information on Enalapril (3 pages), 2001. retrieved from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/18-998s058_Vasotec.cfm.

DRUGS.COM. Enalapril Tablets Soluble. Website [online]. [available online May 9, 2010] [retrieved on Jan. 16, 2014], 11 pages.

Retrieved from the Internet< URL: <https://web.archive.org/web/20100509220009/http://www.drugs.com/pro/enalapril-tablets-soluble.html>>. Enalapril Tablets Soluble—Clinical Pharmacology; Indications and Usage for Enalapril Tablets Soluble; Enalapril Tablets Soluble Dosage and Administration.

European Patent Application No. 13844343.7 Communication dated Mar. 15, 2018.

European Patent Application No. 13844343.7 Extended European Search Report dated Feb. 19, 2016.

European Search Report for EP17767676.4 dated Oct. 8, 2019.

Extended European Search Report dated Feb. 19, 2016, for EP Application No. 13844343.7.

Final Office Action dated Nov. 19, 2019 for U.S. Appl. No. 16/242,898.

Garrett. Prediction of stability of drugs and pharmaceutical preparations. *Journal of Pharmaceutical Sciences* 51(9):811-833 (1962).

US 10,918,621 B2

Page 3

(56)

References Cited

OTHER PUBLICATIONS

Glass et al. Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. *J Pharm Sci* 9(3):398-426 (2006).

Gulf Cooperation Council. The GCC Guidelines for Stability Testing of Drug Substances and Pharmaceutical Products. Publication [online]. Edition Two, 1428 H-2007 G [available online Jul. 2011] [retrieved on Feb. 3, 2014]. Retrieved from the Internet:< URL: https://web.archive.org/web/20110726040053/http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisation/GCC/T_opics_under_Harmonisation/Stability.pdf>. page 22, 2.9 .3; p. 25, 2.9.7. Handbook of Pharmaceutical Excipients, Fifth edition, edited by Raymond C. Rowe et al., London: Pharmaceutical Press, 2006, (monographs for citric acid monohydrate, sodium benzoate, sodium citrate, sodium hydroxide, and xylitol), 23 pages.

Harris, Daniel C. Exploring Chemical Analysis, 4th edition. New York: W.H. Freeman and Company, 2009 (Chapters 8,9,21 and 22), 105 pages.

Hensel et al. Transesterification reactions off parabens (Alkyl 4-Hydroxybenzoates) with polyols in aqueous solution. *J Pharm Sci* 84(1):115-119 (1995).

Hsu et al. Enalapril in Infants With Single Ventricle: Results of a Multicenter Randomized Trial. *Circulation* 122(4):333-340 (2010).
Hsu et al. Rationale and design of a trial of angiotensin-converting enzyme inhibition in infants with single ventricle. *American Heart Journal* 157(1):37-45 (2009).

International Search Report and Written Opinion dated Jun. 16, 2017 for PCT/US17/023074 (WO2017161339).

Kalaitzidis et al. Prehypertension: is it relevant for nephrologists? *Kidney International* 77:194-200 (2010).

Li et al. Lessons learned from a pediatric clinical trial: The Pediatric Heart Network Angiotensin-Converting Enzyme Inhibition in Mitral Regurgitation Study. *American Heart Journal* 161(2):233-240 (2011).

Liern et al., "The additive antiproteinuric effect of Enalapril and Losartan to normotensive patients with pathology proteinuria," *Nefrologia* : publicacion oficial de la Sociedad Espanola Nefrologia (2004), 24(6), 553-8, Database: MEDLINE (with English abstract).
Lima et al., "Stability and in vitro release profile of enalapril maleate from different commercially available tablets: Possible therapeutic implications," *Journ. Pharmac. And Biomed. Analysis*, 47, pp. 934-937 (2008).

Lipshultz, "Exposure to anthracyclines during childhood causes cardiac injury," *Seminars in Oncology* (2006), 33(3, Suppl. 8), S8-S14., Database: CAPLUS, DOI:10.1053/j.seminoncol.2006.04.019.

Ma et al., HPLC and LC-MS studies of the transesterification reaction of Methylparaben with twelve 3- to 6-carbon sugar alcohols and propylene glycol and the isomerization of the reaction products by acyl migration. *Journal of Chromatographic Science*, 40(3):170-177, 2002.

Mc Nahata et al., Stability of enalapril maleate in three extemporaneously prepared oral liquids, *American Journal of Health System Pharmacy*, American Society of Health Systems Pharmacy, US, vol. 55, No. 11, Jun. 1, 1998, pp. 1155-1157.

Meyers et al. Pharmacotherapy Review of Chronic Pediatric Hypertension. *Clinical Therapeutics* (2011), 33(10), 1331-1356. Database: CAPLUS, DOI:10.1016/j.clinthera.2011.09.003.

Miller et al., "Enalapril: a well-tolerated and efficacious agent for the paediatric hypertensive patient," *Journal of hypertension. Supplement : official journal of the International Society of Hypertension* (1986), 4(5), S413-6, Database: MEDLINE.

Miller et al., "Enalapril: a well-tolerated and efficacious agent for the pediatric hypertensive patient," *Journal of cardiovascular pharmacology* (1987), 10 Suppl 7S154-6, Database: MEDLINE.

Mir et al., "Effect of carvedilol on QT duration in pediatric patients with congestive heart failure," *Clinical Drug Investigation* (2004), 24(1), 9-15. Database: CAPLUS, DOI:10.2165/00044011-200424010-00002.

Momma, "ACE inhibitors in pediatric patients with heart failure," *Paediatric drugs* (2006), 8(1), 55-69, Database: MEDLINE.

Nahata et al. Stability of enalapril maleate in three extemporaneously prepared oral liquids. *Am. J. Health-Syst Pharm* 55:1155-1157 (1998).

Nakamura et al., "The kinetic profiles of enalapril and enalaprilat and their possible developmental changes in pediatric patients with congestive heart failure," *Clinical pharmacology and therapeutics* (1994), 56(2), 160-8, Database: MEDLINE.

National institutes of Health. 'MedlinePlus: Hypertension'. Website [online]. [available online May 20, 2012] [retrieved on Jan. 16, 2014], 5 pages. Retrieved from the Internet:< URL: <https://web.archive.org/web/20120520035026/http://www.nlm.nih.gov/medlineplus/ency/article/000468.htm>>.

Nationwide Children's Hospital. 'Enalapril Oral Suspension' Publication [online]. Mar. 29, 2010 [retrieved on Jan. 14, 2014], 1 page. Retrieved from the Internet:< URL: <http://www.nationwidechildrens.org/Document/Get/78785>>.

Nationwide Children's Hospital Pharmacy, Columbus, Ohio, Enalapril Oral Suspension Dosage Form, Mar. 29, 2010, XP055291016.

Niazi, Sarfaraz K. Handbook of Pharmaceutical Manufacturing Formulations: Liquid Products, vol. 3, Second edition. New York: Informa Healthcare USA, Inc., 2009, 400 pages.

Nicolosi et al., The prognostic value of predischARGE quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 trial. *European Heart Journal*, 17:1646-1656, 1996.

Non-Final Office Action dated Jan. 7, 2020, for U.S. Appl. No. 16/177,159.

Novartis AG (Appellants) v. *Torrent Pharmaceuticals Limited, Apotex Inc., Mylan Pharmaceuticals Inc.*, (Appellees), No. 2016-1352, Slip Opinion decided Apr. 12, 2017, 27 pages.

Nunn et al. Formulation of medicines for children. *British Journal of Clinical Pharmacology*, 59:6, pp. 674-676 (2005).

Packer et al., Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation*, 100:2312-1218, 1999.

Parish: How do salt and sugar prevent microbial spoilage?; *Scientific American* (2006).

Patel et al., "Extemporaneous Dosage Form for Oral Liquids," *Pharmacophore*, vol. 2, No. 2, pp. 86-103 (2011).

PCT Patent Application No. PCT/US2013/063096 Written Opinion dated Feb. 20, 2014.

PCT Patent Application No. PCT/US2016/059348 International Search Report and Written Opinion dated Jan. 3, 2017.

PCT Patent Application No. PCT/US2017/023074 International Search Report and Written Opinion dated Jun. 16, 2017.

PCT/US2013/63096 International Search Report and Written Opinion dated Feb. 20, 2014.

Product Information of Bicitra, "Sodium Citrate and Citric Acid Oral Solution USP," 2 pages.

Product Information of Ora-Sweet(1 page, 2013) retrieved from, <http://www.stobec.com/documents/data/8196.pdf>.

Proesmans et al., "Enalapril in children with Alport syndrome," *Pediatric nephrology* (Berlin, Germany) (2004), 19(3), 271-5, Database: MEDLINE.

Proesmans et al., Long-term therapy with enalapril in patients with nephrotic-range proteinuriam, *Pediatric nephrology* (Berlin, Germany) (1996), 10(5), 587-9, Database: MEDLINE.

Proesmans et al., "Enalapril in pediatric patients with Alport syndrome: 2 years' experience," *European Journal of Pediatrics* (2000), 159(6), 430-433. Database: CAPLUS, DOI:10.1007/s004310051301.

Raia, et al., Angiotensin-converting enzyme inhibitors: A Comparative review. *DPIC, The Annuals of Pharmacotherapy*, 24:506-525, 1990.

Ramusovic et al., "Determination of enalapril and enalaprilat in small human serum quantities for pediatric trials by HPLC-tandem mass spectrometry," *Biomedical Chromatography* (2012), 26(6), 697-702. Database: CAPLUS, DOI:10.1002/bmc.1716.

Rezende et al., "Stability and Compatibility Study on Enalapril Maleate Using Thermoanalytical Techniques," *Journ Thermal Analysis and Calorimetry*, 93:3, pp. 881-886 (2008).

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(56)

References Cited

OTHER PUBLICATIONS

Rippley et al., "Pharmacokinetic Assessment of an Oral Enalapril Suspension for Use in Children," Biopharmaceutics and Drug Disposition 21:339-344 (2000).

Rose et al., Stability of Lisinopril syrup (2 mg/mL) extemporaneously compounded from tablets. Int J Pharm Compd. 4(5):398-399 (2000).

Russell, Craig Allen, Paediatric Drug Development:— Reformulation, In Vitro, Genomic and In Vivo Evaluation. Thesis, Apr. 2014, 330 pages.

Schlatter et al., Stability of Enalapril solutions prepared from tablets in sterile water. Australian J. Hospital Pharmacy, 27:395, 1997.

Seikaly. Hypertension in children: an update on treatment strategies. Current Opinion in Pediatrics, 19:170-177, 2007.

Silber et al., "Design and baseline characteristics for the ACE inhibitor after anthracycline (AAA) study of cardiac dysfunction in long-term pediatric cancer survivors," American Heart Journal (2001), 142(4), 577-585. Database: CAPLUS, DOI:10.1067/mhj.2001.118115.

Silber et al., "Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines," Journal of Clinical Oncology (2004), 22(5), 820-828. Database: CAPLUS, DOI:10.1200/JCO.2004.06.022.

Simončić et al., "Use of microcalorimetry in determination of stability of enalapril maleate and enalapril maleate table formulations," Intl. Journ. Pharmaceutics, 342, pp. 145-151 (2007).

Sipahi et al. Effect of Antihypertensive Therapy on Incident Stroke in Cohorts with Prehypertensive Blood Pressure Levels: A Meta-Analysis of Randomized Controlled Trials, Stroke: Journal of the American Heart Association [online], Dec. 8, 2011 (retrieved Jan. 16, 2014], 10 pages. Retrieved from the Internet:< URL:http://www.medpagetoday.com/upload/2011/12/9/Stroke-2011-Sipahi-STROKEAHA.111.636829.pdf>.

Sipahi et al., Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis, J. Am. Coll. Cardiol. 48, 833-838, 2006.

Sosnowska et al., "Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared from Commercially Available Tablets," Acta Polonicae Pharmaceutica, vol. 66, No. 3, pp. 321-326 (2009).

Standing et al. Paediatric formulations—Getting to the heart of the problem. International Journal of Pharmaceutics (2005), 300(1-2), 56-66. Database: CAPLUS.

Stanisz, "Evaluation of stability of enalapril maleate in solid phase," Journ. Pharma. and Biomed. Analysis, 31, pp. 375-380 (2003).

TEVA UK, Limited. Enalapril Maleate 2.5 mg, 5 mg, 10 mg and 20 mg Tablets. Product Brochure [online]. Mar. 2011 [retrieved on Jan. 14, 2014], 8 pages. Retrieved from the Internet:< URL:http://www.drugs.com/uk/pdf/leaflet/213793.pdf>. column 2, lines 70-76.

Thompson et al., Characterization of an extemporaneous liquid formulation of lisinopril. Am J Health Syst Pharm. 60(1):69-74 (2003).

Tian et al., Effect of organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphism on the single- and multiple-dose pharmacokinetics of enalapril in healthy Chinese adult men Clinical Therapeutics, 33(5): 655 (2011).

U.S. Appl. No. 13/670,355 Office Action dated Feb. 8, 2013.

U.S. Appl. No. 13/670,355 Office Action dated Jul. 30, 2013.

U.S. Appl. No. 13/914,452 Office Action dated Aug. 28, 2013.

U.S. Appl. No. 14/433,502 Office Action dated Dec. 29, 2016.

U.S. Appl. No. 14/433,502 Restriction Requirement dated Apr. 12, 2016.

U.S. Appl. No. 14/934,752 First Action Interview dated Jan. 25, 2016.

U.S. Appl. No. 14/934,752 Office Action dated Apr. 26, 2016.

U.S. Appl. No. 15/081,603 First Action Interview dated Sep. 2, 2016.

U.S. Appl. No. 15/081,603 First Action Interview Office Action Summary dated Jan. 17, 2017.

U.S. Appl. No. 15/268,095 Office Action dated Oct. 13, 2016.

U.S. Appl. No. 15/433,743 Office Action dated Jun. 5, 2017.

U.S. Appl. No. 15/483,691 Office Action dated Jun. 8, 2017.

U.S. Appl. No. 15/613,622 Office Action dated Aug. 11, 2017.

U.S. Appl. No. 15/850,732 Office Action dated Mar. 1, 2018.

U.S. Appl. No. 16/003,994 Office Action dated Sep. 20, 2018.

U.S. Appl. No. 16/177,159 Advisory Action dated Sep. 16, 2019.

U.S. Appl. No. 16/177,159 Final Office Action dated Jun. 24, 2019.

U.S. Appl. No. 16/242,898 Office Action dated May 2, 2019.

U.S. Appl. No. 15/802,341 Office Action dated Apr. 19, 2018.

Van Hecken et al. Absence of a pharmacokinetic interaction between enalapril and frusemide British Journal of Clinical Pharmacology, 1987, vol. 23:84-87.

VASOTEC (Enalapril Maleate) Product Insert (2010) 5 pages (Best copy available).

Wang et al., "Eudragit E Accelerated the Diketopiperazine Formation of Enalapril Maleate Determined by Thermal FTIR Microspectroscopic Technique," Pharmaceutical Research, vol. 21, No. 11, Nov. 2004.

Webster et al., The Stability of Lisinopril as an extemporaneous syrup. Int J Pharm Compd. 1(5):352-353 (1997).

Wells et al., "A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension," Journal of Clinical Pharmacology (2002), 42(8), 870-880. Database: CAPLUS, DOI:10.1177/009127002401102786.

Wells et al., "The Pharmacokinetics of Enalapril in Children and Infants with Hypertension," J. Clin Pharmacol 41:1064-1074 (2001).

Williams et al., "Factors affecting growth in infants with single ventricle physiology: a report from the Pediatric Heart Network Infant Single Ventricle Trial," The Journal of Pediatrics (2011), 159(6), 1017-22.e2, Database: MEDLINE.

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FIG. 1

● Enalapril diketopiperazine; ○ Enalaprilat

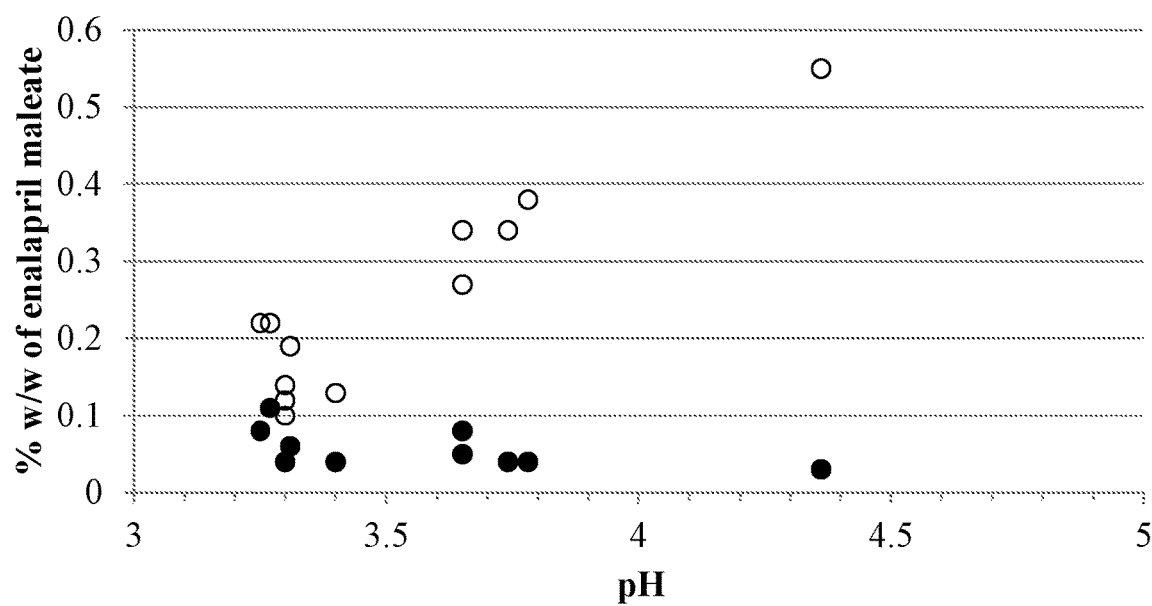
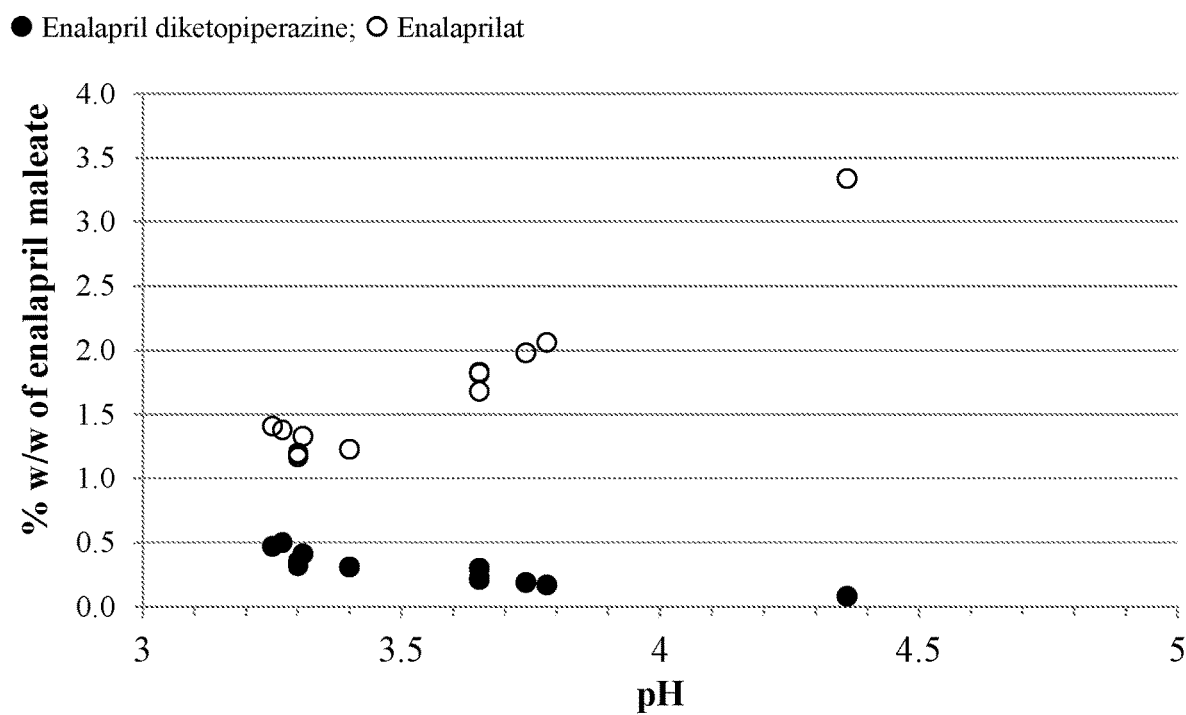


FIG. 2



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ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

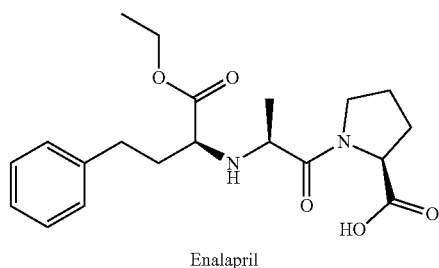
This application is a continuation of U.S. patent application Ser. No. 16/883,553, filed May 26, 2020 which is a continuation of U.S. patent application Ser. No. 16/242,898, filed Jan. 8, 2019, which is a continuation of Ser. No. 16/177,159, filed Oct. 31, 2018, which is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018 (now U.S. Pat. No. 10,154,987, issued Dec. 18, 2018), which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

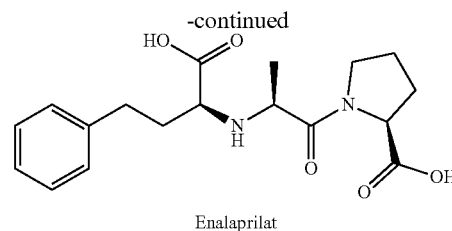
Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralocorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotensin I to angiotensin II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



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Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the

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formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 18 months. In some embodiments, the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some

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embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about $5\pm 3^\circ\text{C}$. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed descrip-

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tion that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treat-

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ment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77

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mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable

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salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thau-matin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003—propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005—maltodextrin, sorbitol, and fructose combination and Product Code 918.010—water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor

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combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), Maltisweet™ (maltitol solution, Ingredion), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

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In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about

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3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w,

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about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w,

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about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and preservative incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

In some embodiments, the oral liquid formulation comprises a buffer.

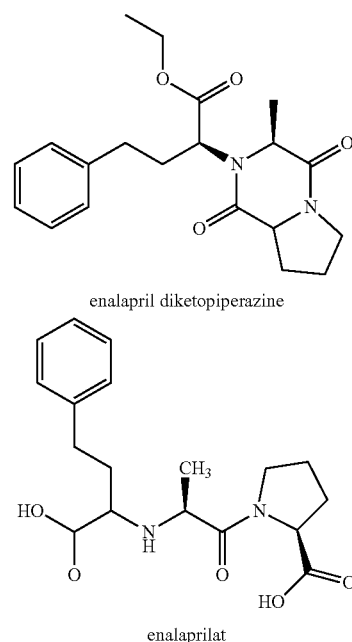
In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises

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citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodi-

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ments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/ml, about 1.31 mg/ml, about 1.32 mg/ml, about 1.33 mg/ml, about 1.34 mg/ml, about 1.35 mg/ml, about 1.36 mg/ml, about 1.37 mg/ml, about 1.38 mg/ml, about 1.39 mg/ml, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/ml, about 1.61 mg/ml, about 1.62 mg/ml, about 1.63 mg/ml, about 1.64 mg/ml, about 1.65 mg/ml, about 1.66 mg/ml, about 1.67 mg/ml, about 1.68 mg/ml, about 1.69 mg/ml, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/ml, about 1.91 mg/ml, about 1.92 mg/ml, about 1.93 mg/ml, about 1.94 mg/ml, about 1.95 mg/ml, about 1.96 mg/ml, about 1.97 mg/ml, about 1.98 mg/ml, about 1.99 mg/ml, or about 2 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/ml, about 2.05 mg/ml, about 2.1 mg/ml, about 2.15 mg/ml, about 2.2 mg/ml, about 2.25 mg/ml, about 2.3 mg/ml, about 2.35 mg/ml, about 2.4 mg/ml, about 2.45 mg/ml, about 2.5 mg/ml, about 2.55 mg/ml, about 2.6 mg/ml, about 2.65 mg/ml, about 2.7 mg/ml, about 2.75 mg/ml, about 2.8 mg/ml, about 2.85 mg/ml, about 2.9 mg/ml, about 2.95 mg/ml, about 3 mg/ml, about 3.05 mg/ml, about 3.1

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mg/ml, about 3.15 mg/ml, about 3.2 mg/ml, about 3.25 mg/ml, about 3.3 mg/ml, about 3.35 mg/ml, about 3.4 mg/ml, about 3.45 mg/ml, or about 3.5 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34% w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1% w/w to about 5% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5% w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/ml, about 0.11 mg/ml, about 0.12 mg/ml, about 0.13 mg/ml, about 0.14 mg/ml, about 0.15 mg/ml, about 0.16 mg/ml, about 0.17 mg/ml, about 0.18 mg/ml, about 0.19 mg/ml, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml,

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about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1% w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural

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or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, pineapple, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w,

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about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is $5\pm 3^{\circ}\text{C}$. In some embodiments, refrigerated condition is about 2°C ., about 2.1°C ., about 2.2°C ., about 2.3°C ., about 2.4°C ., about 2.5°C ., about 2.6°C ., about 2.7°C ., about 2.8°C ., about 2.9°C ., about 3°C ., about 3.1°C ., about 3.2°C ., about 3.3°C ., about 3.4°C ., about 3.5°C ., about 3.6°C ., about 3.7°C ., about 3.8°C ., about 3.9°C ., about 4°C ., about 4.1°C ., about 4.2°C ., about 4.3°C ., about 4.4°C ., about 4.5°C ., about 4.6°C ., about 4.7°C ., about 4.8°C ., about 4.9°C ., about 5°C ., about 5.1°C ., about 5.2°C ., about 5.3°C ., about 5.4°C ., about 5.5°C ., about 5.6°C ., about 5.7°C ., about 5.8°C ., about 5.9°C ., about 6°C ., about 6.1°C ., about 6.2°C ., about 6.3°C ., about 6.4°C ., about 6.5°C ., about 6.6°C ., about 6.7°C ., about 6.8°C ., about 6.9°C ., about 7°C ., about 7.1°C ., about 7.2°C ., about 7.3°C ., about 7.4°C ., about 7.5°C ., about 7.6°C ., about 7.7°C ., about 7.8°C ., about 7.9°C ., or about 8°C . At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. $25\pm 5^{\circ}\text{C}$.; $55\pm 10\%$ RH). In some instances, an accelerated condition is at about 25°C ., about 30°C ., about 35°C ., about 40°C ., about 45°C ., about 50°C ., about 55°C ., or about 60°C . In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40°C ., or 60°C ., at ambient humidity. In yet further instances, an accelerated condition is about 40°C ., at $75\pm 5\%$ RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preser-

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vative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in

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some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

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In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Dekker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some

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embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2x10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

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At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and

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secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic

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and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76 mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

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In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility

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of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxymethamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltiazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, losartan, eprosartan, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a defi-

nition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

“Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

“Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms “patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological

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or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition

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a condition. As used herein, “treat,” “treated,” “treatment,” or “treating” includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at 60° C.	Formulation					
	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were

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transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours at 60° C.	Formulation		
	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula®

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mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Component	C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	° C.	Weeks	C1	C2	C3	C4	C5
Liquid Formulations							
Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
		4	0.02	0.03	0.03	0.03	0.02
		8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.04	0.02	0.02
		4	0.05	0.09	0.11	0.05	0.04
		8	0.08	0.17	0.19		

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TABLE C-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	° C.	Weeks	C1	C2	C3	C4	C5
Liquid Formulations							
Enalaprilat	40	0	0.03	0.04	0.04	0.02	0.02
		4	0.35	0.91	1.10	0.31	0.21
		8	0.65	1.80	2.05		
	5	0	0.18	0.14	0.12	0.13	0.19
		4	0.18	0.15	0.12	0.43	0.53
		8	0.55	0.38	0.34		
	19-23	0	0.18	0.14	0.12	0.13	0.19
		4	1.35	0.83	0.80	1.75	2.29
		8	3.34	2.06	1.98		
	40	0	0.18	0.14	0.12	0.13	0.19
		4	10.49	6.08	6.11	12.30	16.14
		8	24.37	14.12	14.22		

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Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each pow-

dered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations						
Component	D1	D2	D3	D4	D5	D6
Powder Formulation (grams)						
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

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TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	° C.	Weeks	Liquid Formulations					
			D1	D2	D3	D4	D5	D6
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		
	40	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	4.76	4.42	4.76	6.45	5.55	5.24
		8	8.95	8.64	9.61	12.94	12.73	12.18
		12	11.01	10.64	11.41	16.16		
		26	17.18	17.11	18.30	27.36		

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Example E: Stability of Solution Formulations of Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C. ± 3° C., at room temperature (19-23° C.) and at 40° C. ± 2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		

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-continued

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	° C.	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
	19-23	52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
		0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28

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TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	° C.	Weeks	E1	E2	E3	E4	E5
Enalaprilat	40	12	0.58	0.59	0.53	0.51	0.48
		26	1.10	1.10	1.00	0.95	0.97
		52					2.30
		62	3.02	3.04	2.75	2.64	
		0	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76
		8	4.02	3.99	3.99	3.62	3.37
		12	6.72	6.42	6.47	6.00	5.53
		0	0.00	0.00	0.01	0.02	0.00
		4	0.07	0.09	0.10	0.11	0.07
		8	0.12	0.14	0.10	0.13	0.09
		12	0.16	0.15	0.15	0.17	0.14
	19-23	26	0.31	0.30	0.29	0.31	0.27
		52					0.54
		62	0.75	0.75	0.74	0.71	
		0	0.00	0.00	0.01	0.02	0.00
		4	0.65	0.65	0.68	0.70	0.50
		8	1.17	1.19	1.20	1.23	1.03
		12	1.67	1.69	1.72	1.80	1.30
		26	3.36	3.38	3.42	3.57	3.07
		52					6.32
		62	7.99	8.02	8.04	8.57	
		0	0.00	0.00	0.01	0.02	0.00
		4	4.85	4.93	5.19	5.42	3.33
		8	8.08	8.06	8.56	9.01	6.65
		12	10.70	10.48	11.01	11.97	8.14

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. 1 (5° C. \pm 3° C.) and FIG. 2 (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165

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TABLE G-1-continued

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

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Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

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Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered

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via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_{max} were approximately 115% and 109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

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What is claimed is:

1. A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
 - (iii) a preservative, wherein the preservative is a paraben or a mixture of parabens; and
 - (iv) water;
 wherein the formulation optionally comprises a sweetener, a flavoring agent, or both; wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
2. The stable oral liquid formulation of claim 1, comprising a sweetener.
3. The stable oral liquid formulation of claim 1, comprising a flavoring agent.
4. The stable oral liquid formulation of claim 1, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.
5. The stable oral liquid formulation of claim 1, wherein the buffer concentration is about 10 mM to about 20 mM.
6. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH between about 3 and about 4.
7. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH at about 3.3.
8. The stable oral liquid formulation of claim 1, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.
9. The stable oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.
10. The stable oral liquid formulation of claim 1, wherein the preservative is a mixture of parabens.
11. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is methylparaben, ethylparaben, propylparaben, butylparaben, salts thereof, or a combination thereof.
12. The stable oral liquid formulation of claim 1, wherein the preservative is a mixture of methylparaben and propylparaben.
13. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.
14. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation.
15. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.
16. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 2% w/w to about 30% w/w of the solids in the oral liquid formulation.
17. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 18 months.
18. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5\pm 3^\circ$ C. for at least 24 months.

19. A stable oral liquid formulation, consisting essentially of:
- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
 - (iii) a preservative, wherein the preservative is methylparaben, ethylparaben, propylparaben, butylparaben, or a combination thereof; and
 - (iv) water;
- wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
- wherein the formulation is stable at about $5\pm 3^{\circ}$ C. for at least 12 months; and
- wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
20. The stable oral liquid formulation of claim 19, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.
21. The stable oral liquid formulation of claim 19, wherein the buffer concentration is about 10 mM to about 20 mM.
22. The stable oral liquid formulation of claim 19, wherein the buffer maintains the pH between about 3 and about 4.
23. The stable oral liquid formulation of claim 19, wherein the buffer maintains the pH at about 3.3.
24. The stable oral liquid formulation of claim 19, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.

25. The stable oral liquid formulation of claim 19, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.
26. The stable oral liquid formulation of claim 19, wherein the preservative is a mixture of parabens that are selected from methylparaben, ethylparaben, propylparaben, and butylparaben.
27. The stable oral liquid formulation of claim 19, wherein the preservative is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.
28. The stable oral liquid formulation of claim 19, wherein the preservative is present at about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation.
29. The stable oral liquid formulation of claim 19, wherein the preservative is present at about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.
30. A stable oral liquid formulation, consisting essentially of:
- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below;
 - (iii) a preservative, wherein the preservative is methylparaben, ethylparaben, propylparaben, butylparaben, or a combination thereof; and
 - (iv) water;
- wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
- wherein the formulation is stable at about $5\pm 3^{\circ}$ C. for at least 12 months; and
- wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

* * * * *

PTO/AIA/15 (03-13)

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UTILITY PATENT APPLICATION TRANSMITTAL <small>(Only for new nonprovisional applications under 37 CFR 1.53(b))</small>		Attorney Docket No. 43060-707.201	
		First Named Inventor Gerold L. MOSHER	
		Title Enalapril Formulations	
		Express Mail Label No. Electronically filed on March 25, 2016	

APPLICATION ELEMENTS <small>See MPEP chapter 600 concerning utility patent application contents.</small>	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
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*Note: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 must be included in an Application Data Sheet (ADS).
 (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

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WSGR Docket No. 43060-707.201

PATENT APPLICATION
ENALAPRIL FORMULATIONS

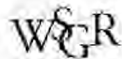
Inventors: Gerold L. Mosher,
Citizen of the United States of America, Residing at
12215 Avila Drive
Kansas City, MO 64145

David W. Miles,
Citizen of the United States of America, Residing at
12309 Wyandotte Street
Kansas City, MO 64145

Assignees: Silvergate Pharmaceuticals, Inc.,
6251 Greenwood Plaza Blvd., Bldg. 6, Suite 101
Greenwood Village, CO 80111

a Delaware Corporation

Entity: Large business concern



Wilson Sonsini Goodrich & Rosati
PROFESSIONAL CORPORATION

650 Page Mill Road
Palo Alto, CA 94304
(650) 493-9300 (Main)
(650) 493-6811 (Facsimile)

Filed Electronically on: March 25, 2016

CLAIMS

WHAT IS CLAIMED IS:

1. An oral liquid formulation, comprising:
 - (i) about 1 mg/ml enalapril maleate;
 - (ii) about 0.70 mg/ml of a sweetener that is sucralose;
 - (iii) a buffer comprising about 1.82 mg/ml citric acid;
 - (iv) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (v) water;
 wherein the pH of the formulation is less than about 3.5; and
 wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.
2. The formulation of claim 1, further comprising a flavoring agent
3. The formulation of claim 1, wherein the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate.
4. The formulation of claim 1, wherein the pH is between about 3 and about 3.5.
5. The formulation of claim 4, wherein the pH is about 3.3.
6. The formulation of claim 1, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.
7. The formulation of claim 6, wherein the citrate concentration in the buffer is about 10 mM.
8. The formulation of claim 1, wherein the formulation is stable at about 5 ± 3 °C for at least 18 months.
9. The formulation of claim 1, wherein the formulation is stable at about 5 ± 3 °C for at least 24 months.
10. The formulation of claim 1, wherein the formulation does not contain mannitol.
11. The formulation of claim 1, wherein the formulation does not contain silicon dioxide.
12. An oral liquid formulation, comprising:
 - (i) about 19.3 % (w/w of solids) enalapril maleate;
 - (ii) about 13.5 % (w/w of solids) of a sweetener that is sucralose;
 - (iii) a buffer comprising about 35.2 % (w/w of solids) citric acid;
 - (iv) about 19.3 % (w/w of solids) of a preservative that is sodium benzoate; and
 - (v) water;
 wherein the pH of the formulation is less than about 3.5; and
 wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.
13. The formulation of claim 12, further comprising a flavoring agent

14. The formulation of claim 12, wherein the buffer further comprises about 2.9 % (w/w of solids) sodium citrate dihydrate.
15. The formulation of claim 12, wherein the pH is between about 3 and about 3.5.
16. The formulation of claim 15, wherein the pH is about 3.3.
17. The formulation of claim 12, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.
18. The formulation of claim 17, wherein the citrate concentration in the buffer is about 10 mM.
19. The formulation of claim 12, wherein the formulation is stable at about 5 ± 3 °C for at least 24 months.
20. An oral liquid formulation, consisting essentially of:
 - (i) about 1 mg/ml enalapril maleate;
 - (ii) about 0.70 mg/ml of a sweetener that is sucralose;
 - (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate;
 - (iv) about 1 mg/ml of a preservative that is sodium benzoate;
 - (v) a flavoring agent; and
 - (vi) water;wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid if needed; and
wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

Document Description: Request First Action Interview

PTO/SB/413C (05-11)

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REQUEST FOR FIRST ACTION INTERVIEW (FULL PILOT PROGRAM)

Attorney Docket Number: 43060-707.201 Application Number (if known): Filed Herewith Filing date: March 25, 2016

First Named Inventor: Gerold L. MOSHER Title: ENALAPRIL FORMULATIONS

APPLICANT HEREBY REQUESTS A FIRST ACTION INTERVIEW IN THE ABOVE-IDENTIFIED APPLICATION. See Instruction Sheet on page 2.

1. The application must contain three (3) or fewer independent claims and twenty (20) or fewer total claims.
2. The application must not contain any multiple dependent claims.
3. By filing this request:

Applicant is agreeing to make an election without traverse if the Office determines that the claims are not obviously directed to a single invention; and

Applicant is agreeing not to request for a refund of the search fee and any excess claims fee paid in the application after the mailing or notification of the pre-interview communication prepared by the examiner.

4. Other attachments: _____

Signature: /Clark Lin/ Date: March 25, 2016
Name (Print/Typed): Clark Y. Lin Registration Number: 67024

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below.

☒ *Total of 1 forms are submitted

The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.201
		Application Number	
Title of Invention	Enalapril Formulations		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

Secrecy Order 37 CFR 5.2:

<input type="checkbox"/>	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
--------------------------	---

Inventor Information:

Inventor	1				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Gerold	L	MOSHER		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	Kansas City	State/Province	MO	Country of Residence	US

Mailing Address of Inventor:

Address 1	12215 Avila Drive				
Address 2					
City	Kansas City	State/Province	MO		
Postal Code	64145	Country	US		

Inventor	2				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	David	W.	MILES		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	Kansas City	State/Province	MO	Country of Residence	US

Mailing Address of Inventor:

Address 1	12309 Wyandotte Street				
Address 2					
City	Kansas City	State/Province	MO		
Postal Code	64145	Country	US		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.

[Add](#)
Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.201
		Application Number	
Title of Invention	Enalapril Formulations		

☐ An Address is being provided for the correspondence information of this application.

Customer Number	21971		
Email Address	patentdocket@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	Enalapril Formulations		
Attorney Docket Number	43060-707.201	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	2	Suggested Figure for Publication (if any)	1

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:
☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	<input type="radio"/> US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	21971		

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.201
		Application Number	
Title of Invention	Enalapril Formulations		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	62/310198	2016-03-18
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX),¹ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country ¹	Filing Date (YYYY-MM-DD)	Access Code ¹ (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

<p>This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.</p> <p><input type="checkbox"/> NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.</p>
--

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.201
		Application Number	
Title of Invention	Enalapril Formulations		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.201
		Application Number	
Title of Invention	Enalapril Formulations		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1	Remove	
<p>If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.</p> <p align="right">Clear</p>		
<input checked="" type="radio"/> Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
<div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
Name of the Deceased or Legally Incapacitated Inventor: <div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>		
Organization Name	Silvergate Pharmaceuticals, Inc.	
Mailing Address Information For Applicant:		
Address 1	5251 Greenwood Plaza Blvd.	
Address 2	Bldg. 6, Suite 101	
City	Greenwood Village	State/Province CO
Country US	Postal Code	80111
Phone Number		Fax Number
Email Address		
Additional Applicant Data may be generated within this form by selecting the Add button. Add		

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.201
		Application Number	
Title of Invention	Enalapril Formulations		

Assignee	1
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Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove				
If the Assignee or Non-Applicant Assignee is an Organization check here. <input type="checkbox"/>				
Prefix	Given Name	Middle Name	Family Name	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1				
Address 2				
City		State/Province		
Country		Postal Code		
Phone Number		Fax Number		
Email Address				

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

[Add](#)**Signature:**[Remove](#)

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet must be signed by a patent practitioner if one or more of the applicants is a juristic entity (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, all joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of all joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Clark Lin/		Date (YYYY-MM-DD)	2016-03-25
First Name	Clark	Last Name	Lin	Registration Number
				67024

Additional Signature may be generated within this form by selecting the Add button.

[Add](#)

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.201
		Application Number	
Title of Invention	Enalapril Formulations		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Doc Code: TRACK1.REQ

Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Gerold L. MOSHER	Nonprovisional Application Number (if known):	
Title of Invention:	ENALAPRIL FORMULATIONS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:
 - I. ☒ **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**
 - i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.
—OR—
 - (b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.
 - ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, or the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.
 - II. ☐ **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**
 - i. A request for continued examination has been filed with, or prior to, this form.
 - ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
 - iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
 - iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
 - v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature <u>/Clark Lin/</u>	Date <u>March 25, 2016</u>
Name (Print/Typed) <u>Clark Y. Lin</u>	Practitioner Registration Number <u>67,024</u>
<p>Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.</p>	
<input checked="" type="checkbox"/> Total of <u>1</u> forms are submitted.	

PTO/A(M)/1 (08-12)

Approved for use through 01/01/2014. CMB 0851-0032

U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no person is required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ENALAPRIL FORMULATIONS
<p>As the below named inventor, I hereby declare that:</p> <p>This declaration is directed to <input type="checkbox"/> The attached application, or <input checked="" type="checkbox"/> United States application or PCT international application number <u>15/081,603</u> filed on <u>March 25, 2016</u></p> <p>The above-identified application was made or authorized to be made by me</p> <p>I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.</p> <p>I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.</p> <p style="text-align: center;">WARNING:</p> <p>Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identify theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.</p>	
LEGAL NAME OF INVENTOR	
Inventor <u>Gerold L. MOSHER</u> Date (Optional) _____	
Signature <u>Gerold L. Mosher</u>	
<p>(Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/A(M)/1 form for each additional inventor.)</p>	

This collection of information is required by 35 U.S.C. 116 and 37 CFR 1.63. The information is required in order to retain a benefit by the public which is justly and by the USPTO to support an application. Confidentiality is governed by 35 U.S.C. 422 and 37 CFR 1.11 and 1.14. The collection is designed to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing this form, call 1-800-PTO-4198 and select option 2.

PTO/AIA/01 (08-12)

Approved for use through 8/31/2014 OMB 0651-0032

U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of invention	ENALAPRIL FORMULATIONS
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As the below named inventor, I hereby declare that:

This declaration is directed to:



The attached application, or

United States application or PCT international application number 15/081,603filed on March 25, 2016

The above-identified application was made or authorized to be made by me

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.273(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTORInventor: David W. MILES

Date (Optional):

3/28/2016

Signature

David W. Miles

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 116 and 37 CFR 1.63. The information is required to obtain or preserve a benefit by the public work in the field (and by the USPTO in process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 7 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the burden of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

(If you need assistance in completing this form, call 1-800-PTO-6196 and select option 2.)



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22311-1450
 www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	CR PART UNIT	FIL FEE REC'D	ATTY DOCKET NO	TOT CLAIMS	INT CLAIMS
15/081,603	03/25/2016		1740	43060-707.201	20	3

CONFIRMATION NO. 3892

FILING RECEIPT



0000000082096018

21971

WILSON, SONSINI, GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050

Date Mailed: 04/12/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Gerold L. MOSHER, Kansas City, MO;
 David W. MILES, Kansas City, MO;

Applicant(s)

Silvergate Pharmaceuticals, Inc., Greenwood Village, CO;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 62/310,198 03/18/2016

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 04/08/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/081,603**

page 1 of 3

Projected Publication Date: 09/21/2017

Non-Publication Request: No

Early Publication Request: No

Title

Enalapril Formulations

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/084,603	03/25/2016	Gerold L. MOSHER	43060-707.201	3892

21971 1590 (09/02/2016)
 WILSON, SONSINI, GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050

EXAMINER
SPRINGER, STEPHANIE K

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
09/02/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

First Action Interview Pilot Program Pre-Interview Communication	Application No.	Applicant(s)	
	15/081,603	MOSHER ET AL.	
	Examiner	Art Unit	AIA (First Inventor to File) Status
	STEPHANIE SPRINGER	1629	Yes

-The MAILING OR NOTIFICATION DATE of this communication appears on the cover sheet with the correspondence address -

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **ONE MONTH OR THIRTY (30) DAYS**, WHICHEVER IS LONGER, FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only ONE additional MONTH.

This communication constitutes notice under 37 CFR 1.136(a)(1)(i).

Applicant must, within the time period for reply, file: (1) A letter requesting not to have a first action interview; (2) A reply under 37 CFR 1.111 waiving the first action interview and First Action Interview Office Action; or (3) An Applicant Initiated Interview Request Form (PTOL-413A) electronically via EFS-Web, accompanied by a proposed amendment or arguments, and schedule the interview within 2 months from the filing of the request. A failure to respond to this communication will be treated as a request not to have an interview. If applicant waives the First Action Interview Office Action, the instant Pre-Interview Communication is deemed the first Office Action on the Merits. The next subsequent Office action may be made final if appropriate. See MPEP 706.07(a).

Status

1) ☒ Responsive to communication(s) filed on 25 March 2016.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

Disposition of Claims

2) ☒ Claim(s) 1-20 is/are pending in the application.

2a) Of the above claim(s) _____ is/are withdrawn from consideration.

3) ☐ Claim(s) _____ is/are allowed.

4) ☒ Claim(s) 1-20 is/are rejected.

5) ☐ Claim(s) _____ is/are objected to.

6) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

7) ☐ The specification is objected to by the Examiner.

8) ☒ The drawing(s) filed on 25 March 2016 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

9) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

Contact Information

Examiner's Telephone Number: (571)270-7380

Examiner's Typical Work Schedule: Monday through Friday, 9 am to 5 pm

Supervisor's Name: Jeffrey Lundgren

Supervisor's Telephone Number: (571)272-5541

Attachment(s) 1) <input type="checkbox"/> Notice of References Cited (PTO-892) 2) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>13 pgs.</u>	3) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date: _____ 4) <input type="checkbox"/> Other: _____
--	---

First Action Interview Pilot Program Pre-Interview Communication		Application No. 15/081,603		Applicant(s) MOSHER ET AL.	
		Examiner STEPHANIE SPRINGER		Art Unit 1629	AIA (First Inventor to File) Status No
Notification of Rejection(s) and/or Objection(s)					
#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection	
1	1-20	013, 043, 028, 036, 037	103	Applicants claim an oral liquid formulation comprising enalapril maleate, sucralose, citric acid, sodium benzoate, and water, wherein the pH is less than about 3.5 and the formulation is stable for at least 12 months.	

Expanded Discussion/Commentary	
	'747 teaches oral liquid compositions comprising enalapril, mannitol, and a sweetener, wherein the oral liquid is formed using a powder formulation, wherein the liquid is stable for at least 36 weeks at ambient or refrigerated conditions. See, e.g., col 3, lines 12-17; col 13, lines 29-33. The composition may comprise additional excipients, including buffering agents such as sodium citrate; preservatives, such as citric acid and benzoic acid; and sweeteners, such as sucralose or branded products such as Ora-Sweet.
	'747 discloses that Ora-Sweet sugar-free flavored syrup is used to solvate or dissolve enalapril. See column 9, lines 34-37. '747 teaches that the enalapril oral liquid compositions encompass both solutions and suspensions, and certain components may be in suspension while others are in solution. See column 11, lines 40-60. Rippley discloses oral liquid formulations comprising 1 mg/mL enalapril. Rippley teaches the preparation of said solution using 10 mL BICITRA, 2 x 20 mg enalapril tablets, and 30 mL Ora-Sweet SF. See p 340, col 2, para 3.
	Rippley teaches that the liquid formulations are referred to as a suspension because the tablet excipients do not fully dissolve, but the active ingredient, enalapril maleate, is in solution. See p 343-344, bridging paragraph. Nahata discloses a composition comprising 1 mg/mL enalapril, citrate buffer, sweetened suspending agent. The composition was prepared from enalapril maleate tablets, citric acid buffer, and a mixture of Ora-Sweet and Ora-Plus. See p 1156, col 1, para 2. The solutions were stable for 91 days at 4 and 25 C.
	Bicitra Sodium Citrate and Citric Acid Oral Solution package insert discloses that Bicitra comprises sodium citrate, citric acid, sodium benzoate, and sorbitol solution. Ora-Sweet package insert discloses that Ora-Sweet comprises sucrose, sorbitol, citric acid, preservatives. Thus, oral liquid compositions comprising 1 mg/mL enalapril maleate, sweeteners such as sucralose, buffers such as citric acid, preservatives such as sodium benzoate, and water were well known at the time of the invention.
	It appears that the instantly claimed invention is reverse engineering the composition which is formed by the dissolution of enalapril maleate tablets in Bicitra and Ora-Sweet. While the prior art does not explicitly teach the recited amounts of each component, it would be within the purview of the ordinarily skilled artisan to optimize the resulting composition, essentially removing the tablet excipients and including the ingredients of Bicitra and Ora-Sweet. While the prior art teaches that the oral liquid composition may be stable for at least 36
	weeks, the prior art is silent with regards to the stability of said solution over a longer period of time. Thus the instantly claimed composition would have been obvious to the skilled artisan. The Examiner suggests presenting evidence demonstrating criticality of the selection of the amounts and specific ingredients, such as evidence demonstrating that the prior art composition does not have the same long term stability as the instantly claimed composition.
DATE:	Stephanie Springer Examiner Art Unit: 1629
	/Jeffrey S Lundgren/ SPE of AU 1629

U.S. Patent and Trademark Office
PTOL-413FP (Rev. 08-13)

First Action Interview Pilot Program - Pre-Interview Communication

Part of Paper No./Mail Date 20160805

Applicant Initiated Interview Request Form

Application No.: 15/081,603 First Named Applicant: Gerold L. Mosher
 Examiner: Stephanie K. Springer Art Unit: 1829 Status of Application: Pre-Interview Communication mailed

Tentative Participants:

(1) Clark Y. Lin (2) Celine Bonnefous
 (3) Gerold L. Mosher (4) _____

Proposed Date of Interview: To be Determined Proposed Time: TBD (☐AM☐PM)

Type of Interview Requested:

(1) ☒ Telephonic (2) ☐ Personal (3) ☐ Video Conference

Exhibit To Be Shown or Demonstrated: ☒ YES ☐ NO

If yes, provide brief description: Comparative data will be shown. Will be submitted prior to the interview.

Issues To Be Discussed

Issues (Rej., Obj., etc)	Claims/ Fig. #s	Prior Art	Discussed	Agreed	Not Agreed
(1) <u>103(a)</u>	<u>1-20</u>	<u>US8568747 Nahata,</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(2) <u>103 (a) cont'd</u>	_____	<u>Bictra, Ora-Sweet, and</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(3) <u>103 (a) cont'd</u>	_____	<u>Ripley et al.</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(4) _____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Continguation Sheet Attached ☐ Proposed Amendment or Arguments Attached

Brief Description of Arguments to be Presented: _____

An interview was conducted on the above-identified application on _____

NOTE: This form should be completed and filed by applicant in advance of the interview (see MPEP § 713.01). If this form is signed by a registered practitioner not of record, the Office will accept this as an indication that he or she is authorized to conduct an interview on behalf of the principal (37 CFR 1.32(a)(3)) pursuant to 37 CFR 1.34. This is not a power of attorney to any above named practitioner. See the Instruction Sheet for this form, which is incorporated by reference. By signing this form, applicant or practitioner is certifying that he or she has read the Instruction Sheet. After the interview is conducted, applicant is advised to file a statement of the substance of this interview (37 CFR 1.133(b)) as soon as possible. This application will not be delayed from issue because of applicant's failure to submit a written record of this interview.

/Clark Lin/

Applicant/Applicant's Representative Signature

Examiner/SPE Signature

Clark Y. Lin

858-350-2318

Typed/Printed Name of Applicant or Representative

Applicant's/Applicant's Representative's Telephone Number

67,024

Registration Number, if applicable

This collection of information is required by 37 CFR 1.133. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 24 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/084,603	03/25/2016	Gerold L. MOSHER	43060-707.201	3892

21971 /590 01/17/2017
 WILSON, SONSINI, GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050

EXAMINER
SPRINGER, STEPHANIE K

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
01/17/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

First Action Interview Office Action Summary	Application No. 15/081,603	Applicant(s) MOSHER ET AL.	
	Examiner STEPHANIE SPRINGER	Art Unit 1629	AIA (First Inventor to File) Status Yes

The MAILING OR NOTIFICATION DATE of this communication appears on the cover sheet with the correspondence address.

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **TWO MONTHS** FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

☐ Applicant's request to not have a first-action interview is acknowledged (or the time period for reply set forth in the Pre-Interview Communication has expired and the Office did not receive any reply).

Status

- 1) ☒ Responsive to communication(s) filed on 25 March 2016 and interview conducted on 14 October 2016.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 3) ☒ Claim(s) 1-20 is/are pending in the application.
3a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 4) ☐ Claim(s) ____ is/are allowed.
- 5) ☒ Claim(s) 1-20 is/are rejected.
- 6) ☐ Claim(s) ____ is/are objected to.
- 7) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 8) ☐ The specification is objected to by the Examiner.
- 9) ☒ The drawing(s) filed on 25 March 2016 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 10) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f)
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

Contact Information

Examiner's Telephone Number: (571)270-7380

Examiner's Typical Work Schedule: Monday through Friday, 9 am to 5 pm

Supervisor's Name: Jeffrey Lundgren

Supervisor's Telephone Number: (571)272-5541

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date 13 pgs.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: ____
- 4) ☒ Other: AF/D. 19 pgs.

First Action Interview Office Action Summary	Application No. 15/081,603		Applicant(s) MOSHER ET AL.	
	Examiner STEPHANIE SPRINGER		Art Unit 1629	AIA (First Inventor to File) Status No

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (If applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
1	1-20	013, 043, 028, 036, 037	112, 2nd	The term "stable" is a relative term, and renders the claims indefinite. It is unclear if stability refers to, e.g., homogeneity, amount of enalapril, amount of precipitation, amount of impurities. Claims do not disclose a standard or threshold of measurement.
2	1-20	013, 043, 028, 036, 037	103	Applicants claim an oral liquid formulation comprising (i) enalapril maleate; (ii) sucralose; (iii) citric acid; (iv) sodium benzoate; (v) water, wherein the pH is less than about 3.5 and the formulation is stable for at least 12 months.

Expanded Discussion/Commentary

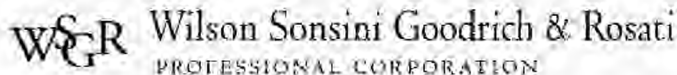
2		747 teaches oral liquid compositions comprising enalapril, mannitol, and sweetener, formed using a powder formulation, wherein the liquid is stable for at least 36 wks at ambient or refrigerated conditions. The oral liquid is prepared by adding an amount of sweetener in liquid form to a powder composition, wherein the powder composition comprises enalapril, mannitol, and colloidal silicon dioxide. The composition may comprise additional excipients, including buffering agents such as sodium citrate; preservatives, such as citric acid and benzoic acid;		
2		and sweeteners, such as sucrose, mannitol, sucralose or branded products such as Ora-Sweet. 747 discloses studies comparing lactose, mannitol, and sucrose as stabilizing agents. Ex1 is directed towards a powder formulation; mannitol is most stable, but the sucrose formulation was also stable. Ex2 is directed towards a solution; 1 mg/mL enalapril w/ mannitol is compared to 2 mg/mL enalapril w/ sucrose. 747 teaches that colloidal silicon dioxide is a glidant, which improve flowability of a powder. When the powder is reconstituted in liquid, the		
2		enalapril and mannitol are in solution while colloidal silicon dioxide forms a suspension. 747 discloses reconstitution of powder composition using Ora-Sweet. The composition w/ colloidal silicon dioxide did not have "clouding"; colloidal silicon dioxide improved flowability of the powder composition. However, additional mixing steps are still required. Rippley and Nahata also disclose compositions reconstituted from enalapril tablets, using Bicitra, Ora-Sweet, and Ora-Plus. Thus, oral liquid compositions comprising 1 mg/mL enalapril maleate, sweeteners		
2		such as mannitol, sucrose, sorbitol, and sucralose; buffers such as citric acid and sodium citrate; preservatives such as sodium benzoate; and water were well known at the time of the invention. The instantly claimed invention differs in that it recites precise amounts of each component. It would be within the purview of the ordinarily skilled artisan to reconstitute enalapril tablets w/ Bicitra, Ora-Sweet, and Ora-Plus and remove components needed for powders or tablets, such as insoluble ingredients. Applicant presents Nahata as the sole comparative		
2		formulation, does not address 747, Rippley, Ora-Sweet, Ora-Plus, Bicitra taken together. Applicant compares Formula E5, i.e. the composition of claim 5, to Nahata. Enalapril tablets are crushed to powder and mixed w/ water, citric acid, sodium citrate, sodium chloride, or mixed w/ 1:1 Ora-Sweet/Ora-Plus. However, the solutions are not filtered. As Examiner stated, a skilled artisan would reverse engineer the tablets dissolved in Ora-Sweet, Ora-Plus, and/or Bicitra and remove unnecessary excipients, i.e., excipients needed for powders or tablets. Proper		
2		comparative example would represent the teachings of the closest prior art as a whole, not just Nahata. Further, the inventive example requires sodium citrate dihydrate, and is not representative of the broadest claimed composition. Applicant is invited to present evidence demonstrating that the amounts of the components taught by Rippley and Nahata, particularly Ora-Sweet, Ora-Plus, and Bicitra, are different from the amounts recited in the instant claims.		

DATE:

/STEPHANIE SPRINGER/
Examiner, Art Unit 1629/JEFFREY S LUNDGREN/
Supervisory Patent Examiner, AU 1629U.S. Patent and Trademark Office
PTOL-413FA (Rev. 11-13)

First Action Interview Office Action Summary

Part of Paper No./Mail Date 20161024



Date: 2016-10-14 09:26:19 PDT

Fax: 15712708380

From: Hicks, Keiko

Subject: Deliver to: Examiner S. Springer

Dear Examiner Springer,

Please see the attached.

Best Regards,

Keiko Hicks

Patent Group Assistant

Wilson Sonsini Goodrich & Rosati

12235 El Camino Real, Suite 200

San Diego, California 92130-3002

858-350-2300

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Las Comas IV, Fifth Floor
Austin, TX 78746-5546
Ph 512-338-5400
Fx 512-338-5499

Beijing

Unit 2901, 29F, Tower C
Beijing Yintai Centre
No. 2 Jianguomenwai Avenue
Chaoyang District, Beijing 100022
People's Republic of China
Ph +86 10 8529 8300
Fx +86 10 8529 8399

Brussels

Rue Montoyer 47
1000 Brussels, Belgium
Ph +32 (0)2 274 57 00
Fx +32 (0)2 274 57 99

Georgetown, DE

Eight West Laurel Street
Georgetown, DE 19847
Ph 302-856-4235
Fx 866-974-7329

Hong Kong

Unit 7001
10/F Henley Building
5 Queen's Road Central
Hong Kong
Ph +852 3972 4965
Fx +852 3972 4999

New York

1301 Avenue of the Americas
40th Floor
New York, NY 10019-6022
Ph 212-999-5800
Fx 212-999-5599

Palo Alto

650 Page Mill Road
Palo Alto, CA 94304-7050
Ph 650-493-9300
Fx 650-493-6811

San Diego

12235 El Camino Real
Suite 200
San Diego, CA 92130-3002
Ph 858-350-2300
Fx 858-350-2399

San Francisco

One Market Plaza
Spear Tower, Suite 3300
San Francisco, CA 94105-1125
Ph 415-947-2000
Fx 415-947-2099

Seattle

701 Fifth Avenue
Suite 5100
Seattle, WA 98104-7036
Ph 206-883-2500
Fx 206-883-2699

Shanghai

Jin Mao Tower
38F, Unit 01
88 Century Boulevard
Pudong, Shanghai 200121
People's Republic of China
Ph +86 21 6165 1700
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Washington, DC

1700 K Street NW, Fifth Floor
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1334248698, 1 of 1 (634)

PAGE 1/19 * RCVD AT 10/14/2016 12:27:11 PM [Eastern Daylight Time] * SVR:W-PTOFAX-002/20 * DNIS:2708380 * CSID:Wilson Sonsini Goodr * DURATION (mm-ss):16-39

Appx109

SLVGT-EPA_0000838



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 Silvergate 43060-707-201
 JGUI; LCD; CBON; RD8; DG8

 Action: 1st Action Interview
 Due: 10/2/16
 Final: 11/2/16

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/034,603	03/25/2016	Gerold L. MOSHER	43060-707-201	3892

21971	7590	09/02/2016
WILSON, SONSINI, GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 94304-1050		

EXAMINER	
SPRINGER, STEPHANIE K.	

ART UNIT	PAPER NUMBER
1809	

NOTIFICATION DATE	DELIVERY MODE
09/02/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocker@wsgr.com

First Action Interview Pilot Program Pre-Interview Communication	Application No.	Applicant(s)	
	15/081,603	MOSHER ET AL.	
	Examiner	Art Unit	AIA (First Inventor to File) Status
	STEPHANIE SPRINGER	1629	Yes

-The MAILING OR NOTIFICATION DATE of this communication appears on the cover sheet with the correspondence address -
THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ONE MONTH OR THIRTY (30) DAYS,
WHICHEVER IS LONGER, FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.
This time period for reply is extendable under 37 CFR 1.136(a) for only ONE additional MONTH.
This communication constitutes notice under 37 CFR 1.136(a)(1)(I).

Applicant must, within the time period for reply, file: (1) A letter requesting not to have a first action interview; (2) A reply under 37 CFR 1.111 waiving the first action interview and First Action Interview Office Action; or (3) An Applicant Initiated Interview Request Form (PTOL-413A) electronically via EFS-Web, accompanied by a proposed amendment or arguments, and schedule the interview within 2 months from the filing of the request. A failure to respond to this communication will be treated as a request not to have an interview. If applicant waives the First Action Interview Office Action, the Instant Pre-Interview Communication is deemed the first Office Action on the Merits. The next subsequent Office action may be made final if appropriate. See MPEP 706.07(a).

Status

1) ☒ Responsive to communication(s) filed on 25 March 2016.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

Disposition of Claims

2) ☒ Claim(s) 1-20 is/are pending in the application.
2a) Of the above claim(s) _____ is/are withdrawn from consideration.

3) ☐ Claim(s) _____ is/are allowed.

4) ☒ Claim(s) 1-20 is/are rejected.

5) ☐ Claim(s) _____ is/are objected to.

6) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

7) ☐ The specification is objected to by the Examiner.

8) ☒ The drawing(s) filed on 25 March 2016 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

9) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.

Contact Information

Examiner's Telephone Number: (571)270-7380
Examiner's Typical Work Schedule: Monday through Friday, 9 am to 5 pm

Supervisor's Name: Jeffrey Lundgren
Supervisor's Telephone Number: (571)272-5541

Attachment(s)	
1) <input type="checkbox"/> Notice of References Cited (PTO-892)	3) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date, _____
2) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>13 pgs</u>	4) <input type="checkbox"/> Other: _____

U.S. Patent and Trademark Office

PTOL-413FP (Rev. 08-13)

First Action Interview Pilot Program - Pre-Interview Communication

Part of Paper No./Mail Date 20160805

First Action Interview Pilot Program Pre-Interview Communication			Application No. 15/081,603	Applicant(s) MOSHER ET AL.	
			Examiner STEPHANIE SPRINGER	Art Unit 1629	AIA (First Inventor to File) Status No
Notification of Rejection(s) and/or Objection(s)					
#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection	
1	1-20	013, 043, 028, 036, 037	103	Applicants claim an oral liquid formulation comprising enalapril maleate; sucralose; citric acid; sodium benzoate; and water, wherein the pH is less than about 3.5 and the formulation is stable for at least 12 months.	

Expanded Discussion/Commentary		
		'747 teaches oral liquid compositions comprising enalapril, mannitol, and a sweetener, wherein the oral liquid is formed using a powder formulation wherein the liquid is stable for at least 36 weeks at ambient or refrigerated conditions. See, e.g., col 3, lines 12-17; col 13, lines 29-33. The composition may comprise additional excipients, including buffering agents such as sodium citrate; preservatives, such as citric acid and benzoic acid; and sweeteners, such as sucralose or branded products such as Ora-Sweet.
		'747 discloses that Ora-Sweet sugar free flavored syrup is used to solvate or dissolve enalapril. See column 8, lines 34-37. '747 teaches that the enalapril oral liquid compositions encompass both solutions and suspensions, and certain components may be in suspension while others are in solution. See column 11, lines 40-60. Rippley discloses oral liquid formulations comprising 1 mg/mL enalapril. Rippley teaches the preparation of said solution using 10 mL BICITRA, 2 x 20 mg enalapril tablets, and 30 mL Ora-Sweet SF. See p 340, col 2, para 3.
		Rippley teaches that the liquid formulations are referred to as a suspension because the tablet excipients do not fully dissolve, but the active ingredient, enalapril maleate, is in solution. See p 343-344, bridging paragraph. Nahata discloses a composition comprising 1 mg/mL enalapril, citrate buffer, sweetened suspending agent. The composition was prepared from enalapril maleate tablets, citric acid buffer, and a mixture of Ora-Sweet and Ora-Plus. See p 1150, col 1, para 2. The solutions were stable for 91 days at 4 and 25 °C.
		Bicitra Sodium Citrate and Citric Acid Oral Solution package insert discloses that Bicitra comprises sodium citrate, citric acid, sodium benzoate, and sorbitol solution. Ora-Sweet package insert discloses that Ora-Sweet comprises sucrose, sorbitol, citric acid, preservatives. Thus, oral liquid compositions comprising 1 mg/mL enalapril maleate, sweeteners such as sucralose, buffers such as citric acid, preservatives such as sodium benzoate, and water were well known at the time of the invention.
		It appears that the instantly claimed invention is reverse engineering the composition which is formed by the dissolution of enalapril maleate tablets in Bicitra and Ora-Sweet. While the prior art does not explicitly teach the recited amounts of each component, it would be within the purview of the ordinarily skilled artisan to optimize the resulting composition, essentially removing the tablet excipients and including the ingredients of Bicitra and Ora-Sweet. While the prior art teaches that the oral liquid composition may be stable for at least 36
		weeks, the prior art is silent with regards to the stability of said solution over a longer period of time. Thus the instantly claimed composition would have been obvious to the skilled artisan. The Examiner suggests presenting evidence demonstrating criticality of the selection of the amounts and specific ingredients, such as evidence demonstrating that the prior art composition does not have the same long term stability as the instantly claimed composition.
DATE:	Stephanie Springer Examiner Art Unit: 1629	Jeffrey S Lundgren/ SPE of AU 1629

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PTOL-413FP (Rev. 08-13)

First Action Interview Pilot Program - Pre-Interview Communication

Part of Paper No./Mail Date 20160805

Approved for use through 07/31/2019 OMB 0651-0031

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Substitute for form 1449/PTO		Complete, if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)		Application Number	15081603
		Filing Date	03-25-2016
		First Named Inventor	MOSHER, Gerold L.
		Art Unit	Not assigned
		Examiner Name	Not assigned
		Attorney Docket Number	43060-707 201
Sheet	1	of	13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ^{2 or known}			
/SKS/	001	US-4374829	02-22-1983	HARRIS, Elbert E. et al.	
/SKS/	002	US-4472380	09-18-1984	HARRIS, Elbert E. et al.	
/SKS/	003	US-4510083	04-09-1985	BLACKLOCK, Thomas J. et al.	
/SKS/	004	US-4743450	05-10-1988	HARRIS, Michael et al.	
/SKS/	005	US-4830853	05-16-1989	MURTHY, Kuchit S. et al.	
/SKS/	006	US-5698562	12-16-1997	MENDES, Robert W. et al.	
/SKS/	007	US-6028222	02-22-2000	DIETLIN, Francois et al.	
/SKS/	008	US-6413988	07-02-2002	DE, Proost Eddy André Josée	
/SKS/	009	US-6977257	12-20-2005	PARAB, Prakash V. et al.	
/SKS/	010	US-7101888	09-05-2006	REO, Joseph P. et al.	
/SKS/	011	US-7605148	10-20-2009	BATTA, Ramesh Babu et al.	
/SKS/	012	US-8153824	04-10-2012	SESHA, Ramesh	
/SKS/	013	US-8568747	10-29-2013	RAJEWSKI, Lian G. et al.	
/SKS/	014	US-8778366	07-15-2014	RAJEWSKI, Lian G. et al.	
/SKS/	015	US-20040171669	09-02-2004	CHENEVIER, Philippe	
/SKS/	016	US-20040258757	12-23-2004	BOSCH, H. William et al.	
/SKS/	017	US-20060094760	05-04-2006	FAWZY, Abdel A. et al.	
/SKS/	018	US-20070265344	11-15-2007	STROBEL, Michael et al.	

Examiner Signature	/Stephanie K Springer/	Date Considered	08/05/2016
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)			Application Number	15081603	
			Filing Date	03-25-2016	
			First Named Inventor	MOSHER, Gerold L.	
			Art Unit	Not assigned	
			Examiner Name	Not assigned	
Sheet	2	of	13	Attorney Docket Number	43060-707 201

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
/SKS/	019	US-20080221156	09-11-2008	SPIREAS, Spiridon	
/SKS/	020	US-20080234291	09-25-2008	FRANCOIS, Marc Karel Jozef et al	
/SKS/	021	US-20090269287	10-29-2009	BERTA, James Albert	
/SKS/	022	US-20100222334	09-02-2010	TALAMONTI, Wayne et al.	
/SKS/	023	US-20140100260	04-10-2014	RAJEWSKI, Lian G. et al.	

FOREIGN PATENT DOCUMENTS						
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		Country Code ¹ Number ² Kind Code ³ (if known)				
/SKS/	001	EP-2903690-A1	08-12-2015	SILVERGATE PHARMACEUTICALS INC [US], et al.	See WO 2014/055667-A1 for full text	<input type="checkbox"/>
/SKS/	002	WO-0145667-A2	06-28-2001	LEK TOVARNA FARMACEVTSKIH [SI], et al.		<input type="checkbox"/>
/SKS/	003	WO-02089775-A1	11-14-2002	ETHYPHARM SA [FR], et al.	In French, with English language abstract	<input checked="" type="checkbox"/>
/SKS/	004	WO-2007070843-A2	06-21-2007	ACUSPHERE INC [US], et al.		<input type="checkbox"/>

Examiner Signature	/Stephanie K. Springer/	Date Considered	08/05/2016
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		Filing Date	03-25-2016
		First Named Inventor	MOSHER, Gerold L.
		Art Unit	Not assigned
		Examiner Name	Not assigned
Sheet	4	of	13
		Attorney Docket Number	43060-707.201

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/SKS/	002	ALLEN et al., "Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids," Am J. Health-Syst Pharm, Vol. 55, pp 1915-1920, (1998).	<input type="checkbox"/>
/SKS/	003	Allen, Lisinopril 1 mg/mL oral liquid US Pharm., 38(2):36-37 (2013).	<input type="checkbox"/>
/SKS/	004	Al-OMARI et al. "Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations " Journal of Pharmaceutical and Biomedical Analysis, Vol. 25:893-902 (2001).	<input type="checkbox"/>
/SKS/	005	BHARDWAJ et al., "Study of forced degradation behavior of enalapril maleate by LC and LC-MS and development of a validated stability-indicating assay method," Journ. Pharm. and Biomed. Analysis, 46, pp 113-120 (2008).	<input type="checkbox"/>
/SKS/	006	BLOWEY, "Update on the pharmacologic treatment of hypertension in pediatrics," Journal of Clinical Hypertension (Hoboken, NJ, United States) 14(6), 383-387 (2012). Database: CAPLUS, DOI:10.1111/j.1751-7176.2012.00659.x.	<input type="checkbox"/>
/SKS/	007	BOURGALT et al., "Reference-based pricing of prescription drugs: exploring the equivalence of angiotensin-converting-enzyme inhibitors," CMAJ, 161:255-60 (1999).	<input type="checkbox"/>
/SKS/	008	CABOT CORPORATION, "Influence of CAB-O-SIL® M-5P on the Angle of Repose and Flow Rates of Pharmaceutical Powders," 10 pages (2004).	<input type="checkbox"/>

Examiner Signature	/Stephanie R Springer/	Date Considered	08/05/2016
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		Examiner Name	Not assigned
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		Attorney Docket Number	43060-707.201

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T ²
/SKS/	009	CALABRO et al., "Hemodynamic effects of a single oral dose of enalapril among children with asymptomatic chronic mitral regurgitation," American Heart Journal (1999), 138(5, Pt. 1), 955-961. Database: CAPLUS, DOI:10.1016/S0002-8703(99)70023-2.	<input type="checkbox"/>
/SKS/	010	Definition of Hypertension (1 page) retrieved from: http://medical-dictionary.thefreedictionary.com/hypertension .	<input type="checkbox"/>
/SKS/	011	DELUCCHI et al., "Enalapril and prednisone in children with nephrotic-range proteinuria," Pediatric nephrology (Berlin, Germany) (2000), 14(12), 1088-91, Database: MEDLINE.	<input type="checkbox"/>
/SKS/	012	Drug Information on Enalapril (3 pages) retrieved from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/18-998s058_Vasotec.cfm	<input type="checkbox"/>
/SKS/	013	DRUGS.COM. Enalapril Tablets Soluble. Website [online]. [available online 09 May 2010] [retrieved on 16 January 2014]. Retrieved from the Internet <URL: https://web.archive.org/web/20100509220009/http://www.drugs.com/pro/enalapril-tablets-soluble.html >. Enalapril Tablets Soluble- Clinical Pharmacology; Indications and Usage for Enalapril Tablets Soluble; Enalapril Tablets Soluble Dosage and Administration.	<input type="checkbox"/>
/SKS/	014	European Patent Application No. 13844343.7 Extended European Search Report dated February 19, 2016.	<input type="checkbox"/>

Examiner Signature	/Stephanie K Springer/	Date Considered	08/05/2016
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		First Named Inventor	MOSHER, Gerald L.
		Art Unit	Not assigned
		Examiner Name	Not assigned
Sheet	6	of	13
		Attorney Docket Number	43060-707.201

NON-PATENT LITERATURE DOCUMENTS			
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/SKS/	015	GLASS et al. Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. Journal of Pharmacy & Pharmaceutical Sciences, 14 December 2006, Vol. 9, No. 3; pages 398-426.	<input type="checkbox"/>
/SKS/	016	Gulf Cooperation Council. The GCC Guidelines for Stability Testing of Drug Substances and Pharmaceutical Products. Publication [online]. Edition Two. 1428 H-2007 G [available online July 2011] [retrieved on 3 February 2014]. Retrieved from the Internet: <URL: https://web.archive.org/web/20110726040053/http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisation/GCC/T_opics_under_Harmonisation/Stability.pdf>; page 22, 2.9.3; page 25, 2.9.7.	<input type="checkbox"/>
/SKS/	017	HSU et al. "Enalapril in Infants With Single Ventricle: Results of a Multicenter Randomized Trial." Circulation (2010), 122(4), 333-340. Database: CAPLUS, DOI:10.1161/CIRCULATIONAHA.109.927888.	<input type="checkbox"/>
/SKS/	018	HSU et al. "Rationale and design of a trial of angiotensin-converting enzyme inhibition in infants with single ventricle." American Heart Journal (2009), 157(1), 37-45. Database: CAPLUS, DOI:10.1016/j.ahj.2008.08.030.	<input type="checkbox"/>
/SKS/	019	KALAITZIDIS et al. Prehypertension: is it relevant for nephrologists?" Kidney International, 2010, 77:194-200.	<input type="checkbox"/>

Examiner Signature	/Stephanie K Springer/	Date Considered	03/05/2016
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Substitute for form 1449/PTO		Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)		Application Number	15081603
		Filing Date	03-25-2016
		First Named Inventor	MOSHER, Gerold L.
		Art Unit	Not assigned
		Examiner Name	Not assigned
		Attorney Docket Number	43060-707.201
Sheet	7	of	13

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/SKS/	020	LI et al., "Lessons learned from a pediatric clinical trial: The Pediatric Heart Network Angiotensin-Converting Enzyme Inhibition in Mitral Regurgitation Study," American Heart Journal (2011), 161(2):233-240, Database: CAPLUS, DOI:10.1016/j.ahj.2010.10.030.	<input type="checkbox"/>
/SKS/	021	LIMA et al., "Stability and in vitro release profile of enalapril maleate from different commercially available tablets: Possible therapeutic implications," Journ. Pharmac. and Biomed. Analysis, 47, pp 934-937 (2008).	<input type="checkbox"/>
/SKS/	022	LIPSHULTZ, "Exposure to anthracyclines during childhood causes cardiac injury," Seminars in Oncology (2006), 33(3, Suppl. 8), S8-S14, Database: CAPLUS, DOI:10.1053/j.seminoncol.2006.04.019.	<input type="checkbox"/>
/SKS/	023	MEYERS et al., "Pharmacotherapy Review of Chronic Pediatric Hypertension," Clinical Therapeutics (2011), 33(10), p.1331-1356, Database: CAPLUS, DOI:10.1016/j.clinthera.2011.09.003.	<input type="checkbox"/>
/SKS/	024	MILLER et al., "Enalapril: a well-tolerated and efficacious agent for the paediatric hypertensive patient," Journal of hypertension. Supplement : official journal of the International Society of Hypertension (1986), 4(5), S413-16, Database: MEDLINE.	<input type="checkbox"/>
/SKS/	025	MILLER et al., "Enalapril: a well-tolerated and efficacious agent for the pediatric hypertensive patient," Journal of cardiovascular pharmacology (1987), 10 Suppl 7S, p.154-56, Database: MEDLINE.	<input type="checkbox"/>

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/SKS/	026	MIR et al., "Effect of carvedilol on QT duration in pediatric patients with congestive heart failure," Clinical Drug Investigation (2004), 24(1), 9-15. Database: CAPLUS, DOI:10.2165/00044011-200424010-00002.	<input type="checkbox"/>
/SKS/	027	MOMMA, "ACE inhibitors in pediatric patients with heart failure," Paediatric drugs (2006), 8(1), 55-69	<input type="checkbox"/>
/SKS/	028	NAHATA et al., "Stability of enalapril maleate in three extemporaneously prepared oral liquids," Am. J. Health-Syst Pharm Vol. 55, pp. 1155-1157 (1998)	<input type="checkbox"/>
/SKS/	029	NAKAMURA et al., "The kinetic profiles of enalapril and enalaprilat and their possible developmental changes in pediatric patients with congestive heart failure," Clinical pharmacology and therapeutics (1994), 56(2), 160-8.	<input type="checkbox"/>
/SKS/	030	National Institutes of Health. 'MedlinePlus: Hypertension'. Website [online]. [available online 20 May 2012] [retrieved on 16 January 2014]. Retrieved from the Internet: <URL:https://web.archive.org/web/20120520035026/http://www.nlm.nih.gov/medlineplus/ency/article/000468.htm>.	<input type="checkbox"/>
/SKS/	031	Nationwide Children's Hospital. 'Enalapril Oral Suspension' Publication [online]. 29 March 2010 [retrieved on 14 January 2014]. Retrieved from the Internet: <URL:http://www.nationwidechildrens.org/Document/Get/78785>.	<input type="checkbox"/>

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		Filing Date	03-25-2016
		First Named Inventor	MOSHER, Gerold L.
		Art Unit	Not assigned
		Examiner Name	Not assigned
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		Attorney Docket Number	43060-707.201

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/SKS/	032	NUNN et al., "Formulation of medicines for children," British Journal of Clinical Pharmacology, 59:6, pp 674-676 (2005).	<input type="checkbox"/>
/SKS/	033	PATEL et al., "Extemporaneous Dosage Form for Oral Liquids," Pharmacophore, Vol. 2, No. 2, pp. 86-103 (2011).	<input type="checkbox"/>
/SKS/	034	PCT/US2013/63096 International Preliminary Report on Patentability issued April 7, 2015.	<input type="checkbox"/>
/SKS/	035	PCT/US2013/63096 International Search Report and Written Opinion dated February 20, 2014.	<input type="checkbox"/>
/SKS/	036	Product Information of Bicitra, "Sodium Citrate and Citric Acid Oral Solution USP." 2 pages.	<input type="checkbox"/>
/SKS/	037	Product Information of Ora-Sweet (1 page) retrieved from, http://www.stobec.com/documents/data/8196.pdf .	<input type="checkbox"/>
/SKS/	038	PROESMANS et al., "Enalapril in children with Alport syndrome," Pediatric nephrology (Berlin, Germany) (2004), 19(3), 271-75.	<input type="checkbox"/>
/SKS/	039	PROESMANS et al., "Long-term therapy with enalapril in patients with nephrotic-range proteinuriam," Pediatric nephrology (Berlin, Germany) (1996), 10(5), 587-89.	<input type="checkbox"/>

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		Filing Date	03-25-2016
		First Named Inventor	MOSHER, Gerald L.
		Art Unit	Not assigned
		Examiner Name	Not assigned
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/SKS/	040	PROSEMANS et al., "Enalapril in pediatric patients with Alport syndrome: 2 years' experience," European Journal of Pediatrics (2000), 159(6), 430-433. Database: CAPLUS, DOI:10.1007/s004310051301.	<input type="checkbox"/>
/SKS/	041	RAMUSOVIC ET AL., "Determination of enalapril and enalaprilat in small human serum quantities for pediatric trials by HPLC-tandem mass spectrometry," Biomedical Chromatography (2012), 26(6), 697-702. Database: CAPLUS, DOI:10.1002/bmc.1716.	<input type="checkbox"/>
/SKS/	042	REZENDE et al., "Stability and Compatibility Study on Enalapril Maleate Using Thermoanalytical Techniques," Journ Thermal Analysis and Calorimetry, 93:3, pp 881-886 (2008).	<input type="checkbox"/>
/SKS/	043	RIPPLEY et al., "Pharmacokinetic Assessment of an Oral Enalapril Suspension for Use in Children," Biopharmaceutics & Drug Disposition, 21:339-344 (2000).	<input type="checkbox"/>
/SKS/	044	SANDOZ, Limited, Amoxicillin 125 mg/5 ml Powder for Oral Suspension. Product brochure [online]. July 2012, 3 pages. [retrieved on 17 January 2014]. Retrieved from the Internet <URL:http://www.drugs.com/uk/pdf/leaflet/196044.pdf>.	<input type="checkbox"/>
/SKS/	045	SILBER et al., "Design and baseline characteristics for the ACE inhibitor after anthracycline (AAA) study of cardiac dysfunction in long-term pediatric cancer survivors," American Heart Journal (2001), 142(4):577-585. Database: CAPLUS, DOI:10.1067/mhj.2001.118115.	<input type="checkbox"/>

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		First Named Inventor	MOSHER, Gerold L.
		Art Unit	Not assigned
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/SKS/	046	SILBER et al., "Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines," Journal of Clinical Oncology (2004), 22(5), 820-828. Database: CAPLUS, DOI:10.1200/JCO.2004.06.022.	<input type="checkbox"/>
/SKS/	047	SIMONČIČ et al., "Use of microcalorimetry in determination of stability of enalapril maleate and enalapril maleate table formulations," Int'l. Journ. Pharmaceutics, 342, pp. 145-151 (2007).	<input type="checkbox"/>
/SKS/ /SKS/	048	SIPAHI et al. Effect of Antihypertensive Therapy on Incident Stroke in Cohorts with Prehypertensive Blood Pressure Levels: A Meta-Analysis of Randomized Controlled Trials, Stroke: Journal of the American Heart Association (online), 8 December 2011 (retrieved 16 January 2014). Retrieved from the Internet: <URL:http://www.medpagetoday.com/upload/2011/12/9/Stroke-2011-Sipahi-STROKEAHA.111.636829.pdf>.	<input type="checkbox"/>
/SKS/	049	SIPAHI et al., "Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis, J. Am. Coll. Cardiol. 48, 833-838, 2006.	<input type="checkbox"/>
	050	SOSNOWSKA et al., "Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared from Commercially Available Tablets," Acta Poloniae Pharmaceutica, Vol. 66, No. 3, pp. 321-326 (2009).	<input type="checkbox"/>
/SKS/	051	STANDING et al., "Paediatric formulations-Getting to the heart of the problem," International Journal of Pharmaceutics (2005), 300(1-2), 56-66.	<input type="checkbox"/>

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/SKS/	052	STANISZ, "Evaluation of stability of enalapril maleate in solid phase," Journ. Pharma. and Biomed. Analysis, 31, pp 375-380 (2003).	<input type="checkbox"/>
/SKS/	053	TEVA UK, Limited, Enalapril Maleate 2.5 mg, 5 mg, 10 mg and 20 mg Tablets. Product Brochure [online]. March 2011 [retrieved on 14 January 2014]. Retrieved from the internet: <URL:http://www.drugs.com/uk/pdf/leaflet/213793.pdf>. column 2, lines 70-76.	<input type="checkbox"/>
/SKS/	054	Tian et al., Effect of organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphism on the single- and multiple-dose pharmacokinetics of enalapril in healthy Chinese adult men. Clinical Therapeutics, 33(5):655 (2011).	<input type="checkbox"/>
/SKS/	055	U.S. Patent Application No. 13/670,355 Office Action dated February 8, 2013.	<input type="checkbox"/>
/SKS/	056	U.S. Patent Application No. 13/670,355 Office Action dated July 30, 2013.	<input type="checkbox"/>
/SKS/	057	U.S. Patent Application No. 14/934,752 First Action Interview dated January 25, 2016.	<input type="checkbox"/>
/SKS/	058	VAN HECKEN et al. "Absence of a pharmacokinetic interaction between enalapril and frusemide." British Journal of Clinical Pharmacology, 1987, Vol. 23:84-87.	<input type="checkbox"/>
/SKS/	059	VASOTEC (Enalapril Maleate) Product Insert (2010), 2 pages.	<input type="checkbox"/>

Examiner Signature	/Stephanie K Springer/	Date Considered	08/05/2016
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Substitute for form 1449/PTC		Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)		Application Number	15081603
		Filing Date	03-25-2016
		First Named Inventor	MOSHER, Gerold L.
		Art Unit	Not assigned
		Examiner Name	Not assigned
Sheet	13	of	13
		Attorney Docket Number	43060-707.201

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T ²
/SKS/	060	WANG et al., "Eudragit E Accelerated the Diketopiperazine Formation of Enalapril Maleate Determined by Thermal FTIR Microspectroscopic Technique," Pharmaceutical Research, Vol. 21, No. 11, p. 2127-2132, November 2004.	<input type="checkbox"/>
/SKS/	061	WELLS et al., "A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension," Journal of Clinical Pharmacology (2002), 42(8), 870-880. Database: CAPLUS, DOI:10.1177/009127002401102786.	<input type="checkbox"/>
/SKS/	062	WELLS et al., "The Pharmacokinetics of Enalapril in Children and Infants with Hypertension," J. Clin Pharmacol 41:1064-1074 (2001).	<input type="checkbox"/>
/SKS/	063	WILLIAMS et al., "Factors affecting growth in infants with single ventricle physiology: a report from the Pediatric Heart Network Infant Single Ventricle Trial," The Journal of Pediatrics (2011), 159(6), 1017-1022.	<input type="checkbox"/>

Examiner Signature	/Stephanie K Springer/	Date Considered	08/05/2016
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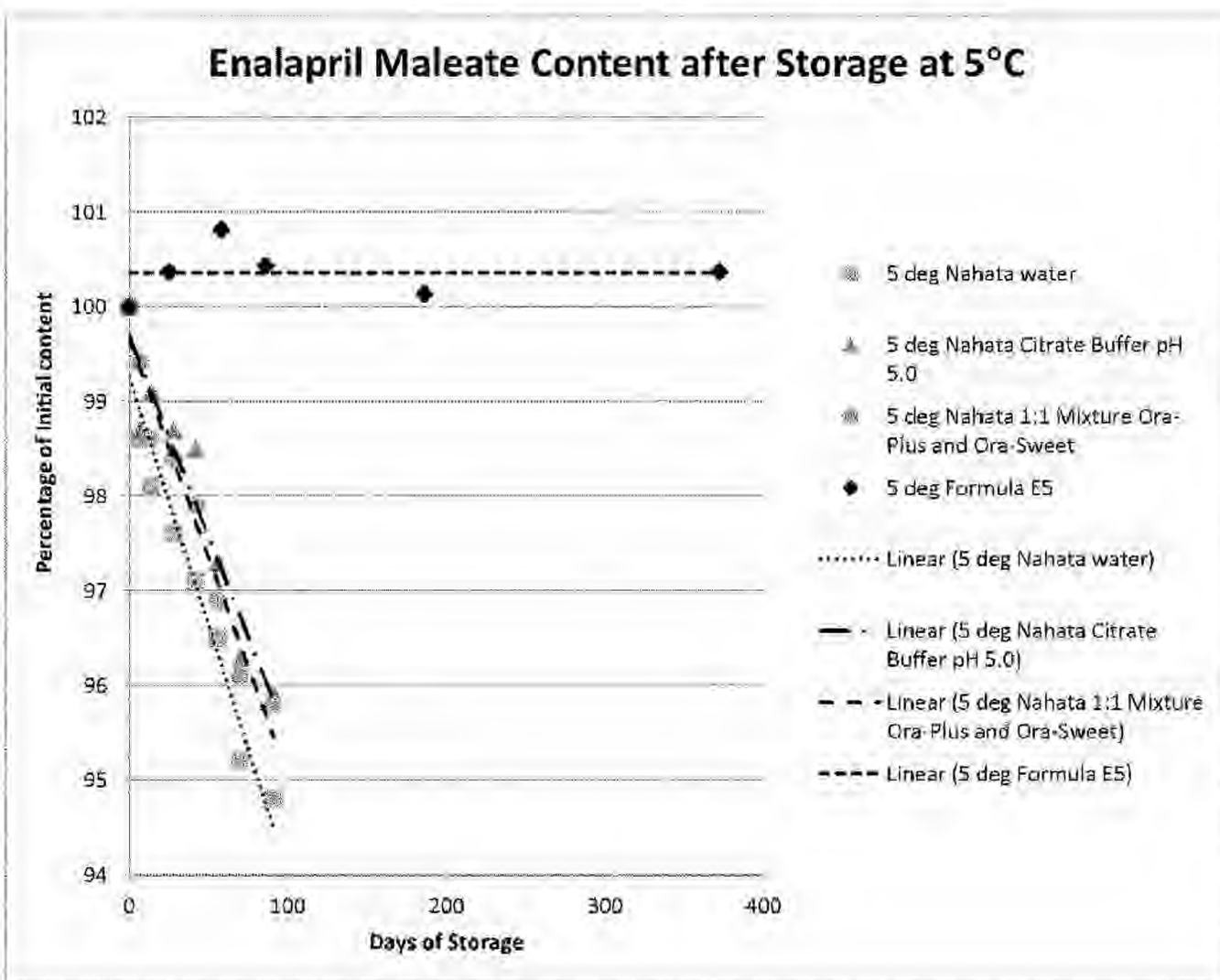
U.S. Patent Application No. 15/081,603

Attorney Docket No. 43060-707.201

INTERVIEW EXHIBIT

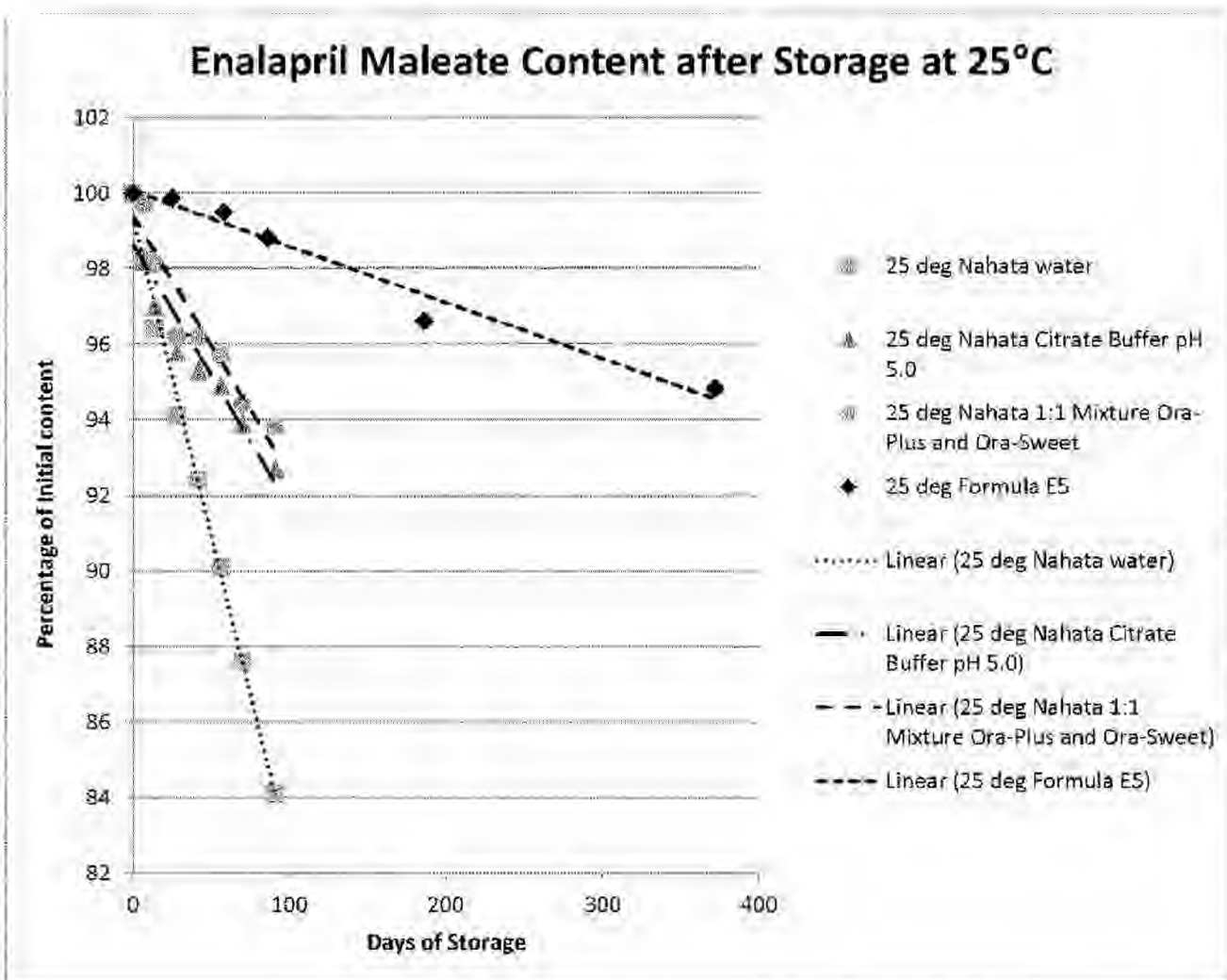
The Office contends that Nahata *et al.* ("Stability of enalapril maleate in three extemporaneously prepared oral liquids" Am. J. Health-Syst Pharm Vol. 55, pp 1155-1157) teaches an oral liquid enalapril formulation (prepared from crushed enalapril maleate tablets) stable for about 90 days.

The stability data at 5 °C and 25 °C published by Nahata *et al.* are plotted graphically below with linear regression of the data for extrapolation. Also included are the enalapril concentrations from Formula E5 of the instant application which comprises citric acid, sodium citrate, sodium benzoate, and sucralose.



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At 5 °C and 25 °C the Nahata formulations are only stable for about 100 days (stability is defined as no more than 5% formation of degradants or 5% loss of enalapril). In contrast, formulation E5 of the instant application is stable for about one year at 5 °C and at 25 °C.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 3892
Serial No.: 15/081,603	Examiner: Stephanie K. Springer
Filed: March 03, 2016	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached response and all marked attachments are being deposited by Electronic Filing on February 3, 2017, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u>/Rose Andico /</u> Rose Andico</p>

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AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION
DATED JANUARY 17, 2017

Commissioner:

Applicant hereby submits a response to the Office Action dated January 17, 2017 (the "Office Action"), in the above-identified application. Applicant respectfully requests amendment of the patent application, and reconsideration and allowance of the pending claims.

Amendments to the Claims begins on page 2.

Remarks begin on page 5.

The Conclusion is on page 23.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed.

Listing of the Claims:

- 1 (Currently Amended) ~~An~~ A stable oral liquid formulation, comprising:
 - (i) about 1 mg/ml enalapril maleate;
 - (ii) about 0.70 mg/ml of a sweetener that is sucralose;
 - (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate;
 - (iv) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (v) water,
 wherein the pH of the formulation is less than about 3.5; and
 wherein the formulation is stable at about 5 ± 3 °C for at least 12 months,
wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.
2. (Original) The formulation of claim 1, further comprising a flavoring agent.
3. (Cancelled)
4. (Original) The formulation of claim 1, wherein the pH is between about 3 and about 3.5.
5. (Original) The formulation of claim 4, wherein the pH is about 3.3.
6. (Original) The formulation of claim 1, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.
7. (Original) The formulation of claim 6, wherein the citrate concentration in the buffer is about 10 mM.
8. (Original) The formulation of claim 1, wherein the formulation is stable at about 5 ± 3 °C for at least 18 months.
9. (Original) The formulation of claim 1, wherein the formulation is stable at about 5 ± 3 °C for at least 24 months.

10. (Original) The formulation of claim 1, wherein the formulation does not contain mannitol.
11. (Original) The formulation of claim 1, wherein the formulation does not contain silicon dioxide.
12. (Currently Amended) ~~An~~ A stable oral liquid formulation, comprising:
 - (i) about 19.3 % (w/w of solids) enalapril maleate;
 - (ii) about 13.5 % (w/w of solids) of a sweetener that is sucralose;
 - (iii) a buffer comprising about 35.2 % (w/w of solids) citric acid and about 2.9 % (w/w of solids) sodium citrate dihydrate;
 - (iv) about 19.3 % (w/w of solids) of a preservative that is sodium benzoate; and
 - (v) water;
 wherein the pH of the formulation is less than about 3.5; and
 wherein the formulation is stable at about 5 ± 3 °C for at least 12 months;
wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.
13. (Original) The formulation of claim 12, further comprising a flavoring agent.
14. (Cancelled).
15. (Original) The formulation of claim 12, wherein the pH is between about 3 and about 3.5.
16. (Original) The formulation of claim 15, wherein the pH is about 3.3.
17. (Original) The formulation of claim 12, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.
18. (Original) The formulation of claim 17, wherein the citrate concentration in the buffer is about 10 mM.
19. (Original) The formulation of claim 12, wherein the formulation is stable at about 5 ± 3 °C for at least 24 months.
20. (Currently Amended) ~~An~~ A stable oral liquid formulation, consisting essentially of:
 - (i) about 1 mg/ml enalapril maleate;
 - (ii) about 0.70 mg/ml of a sweetener that is sucralose;
 - (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate;

- (iv) about 1 mg/ml of a preservative that is sodium benzoate;
- (v) a flavoring agent; and
- (vi) water;

wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid if needed; and

wherein the formulation is stable at about 5 ± 3 °C for at least 12 months;

wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

REMARKS**Status of the Claims**

Claims 1, 12 and 20 have been amended and claims 3 and 14 have been cancelled. Upon entry of the proposed amendment, claims 1-2, 4-13 and 15-20 will be under examination. Support for the amendments to the claims is found in the original claims and throughout the specification, including for example, para. [0080]. No new matter is presented by way of the amendments.

First Action Interview

Applicant would like to extend thanks to Examiners Springer and Lundgren for the telephonic interview on October 14, 2016 with Applicant's representative, Clark Lin and inventor, Gerold Mosher. The pending claims were discussed along with potential rejections. Applicant and the Examiners further discussed potential prior art references and the differences from the claimed subject matter. Although no agreement was reached at that time and Examiner Springer indicated that she would issue a formal Office Action, Applicant feels that the discussion was helping in the preparation of this response and claim amendments.

Claim Rejection - 35 U.S.C. § 112(b)

Claims 1-20 are rejected under 35 U.S.C. 112(b) as allegedly being indefinite. More specifically, the Office alleges that it is unclear if stability refers to e.g., homogeneity, amount of enalapril, amount of precipitation, amount of impurities. Applicant respectfully disagrees but in order to solely advance prosecution, Applicant has amended claims 1, 12, and 20 to add: "wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period". This amendment is supported, for example, in para. [0080] of the instant application. Applicant respectfully requests the withdrawal of this rejection.

Claim Rejection - 35 U.S.C. § 103

Claims 1-20 are rejected under 35 U.S.C. 103 as allegedly being unpatentable over US Pat. No. 8,568,747 ("the '747 patent"), Nahata et al. (Stability of Enalapril Maleate in three Extemporaneously Prepared Oral Liquids) ("Nahata"), Product Information of Bicitra (Sodium

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Attorney Docket No. 43060-707-201

Citrate and Citric Acid Oral Solution) (“Bicitra”), Product Information of Ora-Sweet (“Ora-sweet”), and Rippley et al. (Pharmacokinetics Assessment of an Oral Enalapril Suspension for Use in Children) (“Rippley”).

Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

- (A) Ascertaining the scope and content of the prior art; and
- (B) Ascertaining the differences between the claimed invention and the prior art; and
- (C) Resolving the level of ordinary skill in the pertinent art.

See Graham v. John Deere Co., 383 U.S. 1, (1966); *see also* M.P.E.P. § 2141(II).

Once these factual inquiries have been completed, the Office must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art. According to the M.P.E.P., “The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.” M.P.E.P. § 2141(III). Moreover, the result of any obviousness inquiry must, generally, provide a predictable result or have an expectation of success. *See id.*

The Office asserts that:

747 teaches oral liquid compositions comprising enalapril, mannitol, and sweetener, formed using a powder formulation, wherein the liquid is stable for at least 36 wks [sic] at ambient or refrigerated conditions.

Rippley and Nahata also disclose compositions reconstituted from enalapril tablets, using Bicitra, Ora-Sweet, and Ora-Plus.

Office Action, page 2.

The Office concludes that:

Thus, oral liquid compositions comprising 1 mg/ml enalapril maleate, sweeteners such as mannitol, sucrose, sorbitol, and sucralose; buffers such as citric acid and sodium citrate; preservatives such as sodium benzoate; and water were well known at the time of the invention.

Id., page 2.

The current standard of obviousness takes into account (1) whether there would have been a “reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;” and (2) whether the combination of elements would have yielded “predictable results” *i.e.*, whether there would have been a reasonable expectation of success. (See *e.g.*, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007), *see also PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007) (“The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.”) (emphasis added, internal quotations omitted)).

With regard to the instant claims, Applicant respectfully submits that the Office has not established a *prima facie* case of obviousness. Specifically, Applicant respectfully submits that US 8,568,747, Nahata, Bicitra, Ora-sweet, and Rippley do not provide or suggest all the elements of the claims. Moreover, the cited references have not provided any reason to single out the specific components at the requisite concentrations for a pharmaceutical liquid recited in the instant claims, and further that US 8,568,747, Nahata, Bicitra, Ora-sweet, and Rippley do not provide the legally required reasonable expectation of success. Applicant further submits an Inventor Declaration by Dr. Gerold Mosher (“Mosher Declaration”), with evidence to overcome the obviousness rejection asserted in the Office Action, as discussed in greater detail below.

A. The Cited References Alone or in Combination Do Not Teach All the Elements of the Claimed Stable Enalapril Oral Liquid Formulations

None of the Cited References Teach Enalapril Formulations that are Stable at about 5 ± 3 °C for at Least 12 Months

Applicant respectfully points out that the instant application is directed to novel stable enalapril oral liquid formulations with excellent stability and uniformity properties where the formulation is stable at about 5 ± 3 °C for at least 12 months. Specifically, claim 1 is directed to a stable oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70

mg/ml of a sweetener that is sucralose, (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate, (iv) about 1 mg/ml of a preservative that is sodium benzoate and water at a pH of less than about 3.5. Claim 12 recites a formulation similarly in a % w/w format, and claim 20 recites a formulation similarly in a 'consisting essentially of' format. Further, the stable enalapril oral liquid formulations of these claims represent an elegant solution over the previous methods (extemporaneous and powder for reconstitution) of obtaining liquid enalapril formulations, namely grinding or crushing commercially available enalapril tablets and then suspending the ground tablets in a liquid vehicle or mixing and dissolving a powder for reconstitution with a diluent.

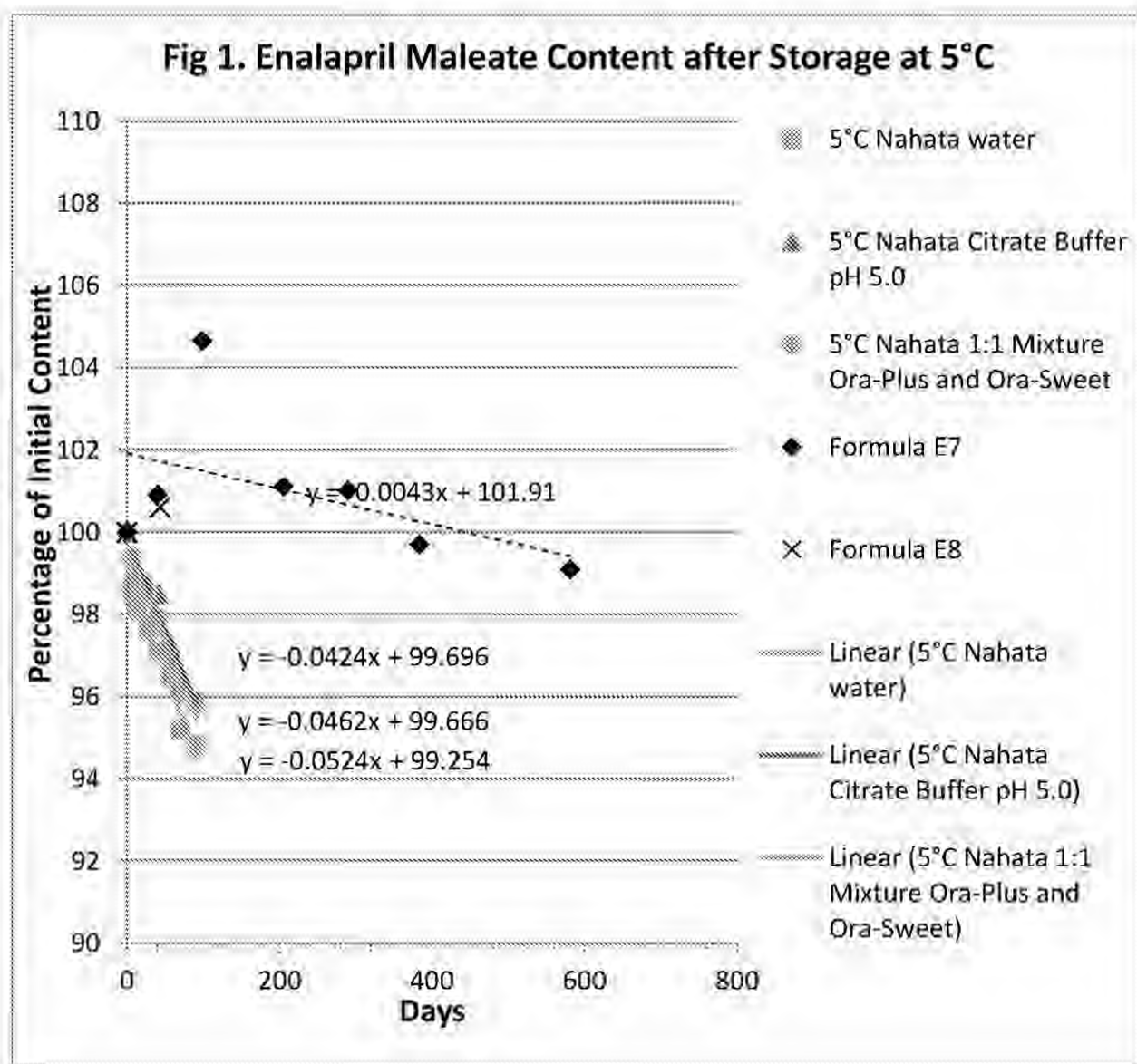
As pointed from above, the claims require that the formulations are stable at about 5 ± 3 °C for at least 12 months. Applicant respectfully points out that, according to the present specification,

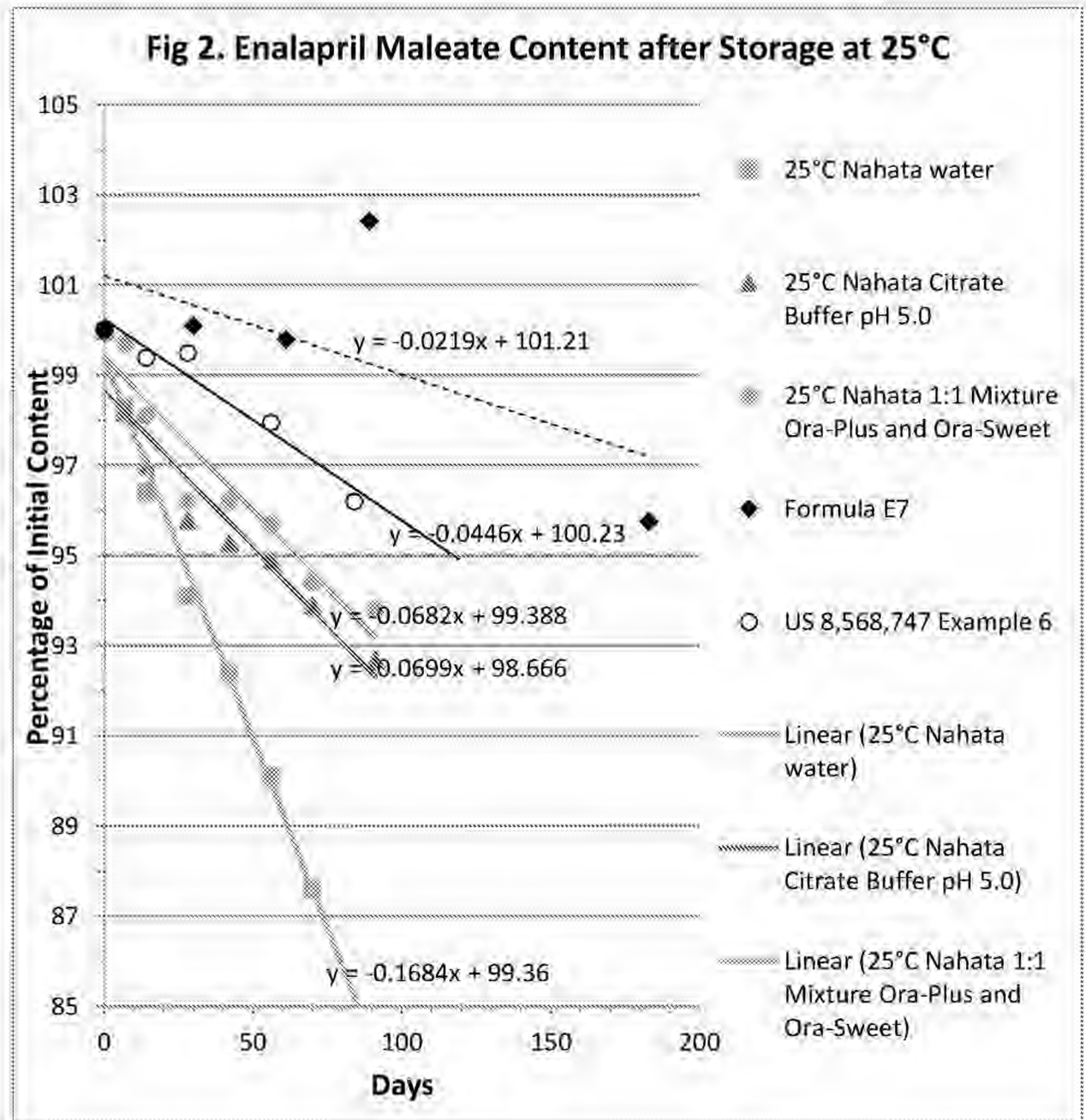
Stable as used herein refer to enalapril oral liquid formulations having about 95 % or greater of the initial enalapril amount and about 5 % w/w or less total impurities or related substances at the end of a given storage period.

Specification, ¶ [0080].

This stability is required by the claims for at least a duration of 12 months at about 5 ± 3 °C. The Specification and Drawings of the instant application provide support and evidence of this stability in, for example, Table E-2 depicting very little amounts of diketopiperazine or enalaprilat degradants formed in the E3, E5 and E6 formulations when stored at 5 °C. Table E-1 depicts that E3, E5 and E6 formulations contain enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water, which Applicant notes are the claimed components of the instant claims, albeit at different concentrations.

Moreover, the Mosher Declaration provides additional data supporting the claimed stability by comparing the dramatic differences in stability between the enalapril oral liquid formulations of the present claims with the stability of the enalapril liquid preparations in Nahata and the '747 patent. In the Mosher Declaration, Mosher plotted graphically with linear regression of the data for extrapolation of the available refrigerated (4 or 5 °C) and room temperature (25 °C) stability data published by Nahata and the '747 patent as well as E7 and E8 enalapril formulations, which is or very similar to the formulation of the instant claims:





The Mosher Declaration also compares the percentage of enalapril between the above formulations in the following tables.

Table A: Enalapril content in formulations after storage at 4 or 5 °C¹

	Nahata				
Days	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	E7	E8
0	100	100	100	100	100
7	98.6	98.7	99.4		
14	98.1	99.1	98.6		
28	97.6	98.7	98.4		
40				100.9	
42	97.1	98.5	97.9		100.3
56	96.5	97.3	96.9		
70	95.2	96.3	96.1		
91	94.8	95.9	95.8		
99				104.7	
205				101.1	
290				101.0	
383				99.7	
581				99.1	

Table B: Enalapril content in formulations after storage at 25 °C

	Nahata			US 8,568,747	
Days	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	Example 6	E7
0	100	100	100	100	100
7	98.3	98.2	99.7		
14	96.4	97	98.1	99.4	
28	94.1	95.8	96.2	99.5	
30					100.1
42	92.4	95.3	96.2		
56	90.1	94.9	95.7	97.9	
61					99.8

At refrigerated and room temperature conditions, the enalapril liquid formulations of Nahata is not stable as there is a loss of nearly 5% after only 91 days refrigerated and 28 days at

¹ Mosher notes that the '747 patent does not provide stability data of the reconstituted liquid formulation at 4 or 5 °C.

25°C. The enalapril concentration in these Nahata preparations decrease rapidly as evidenced by the linear regression in Figs. 1 and 2. Similarly, the reconstituted enalapril liquid formulation of the '747 patent shows that there is a loss of about 5% around 100 days at 25 °C.

Thus, the data presented in the Mosher Declaration clearly demonstrates that the extemporaneous preparations of Nahata and the reconstituted preparations of '747 patent do not meet the stability requirements of the present claims. In contrast, the E7 formulation demonstrates no loss of enalapril for at least 12 months at 5 °C and about 100 days at 25 °C. Further, while the E8 formulation has only one data point, it is expected to track similarly to E7 in terms of stability.

As such, Nahata and the '747 patent do not disclose or suggest any liquid formulations of enalapril having this stability at *about 5 ± 3 °C for at least 12 months* nor any methods of achieving this stability. None of the other cited references, Bicitra, Ora-sweet, and Rippley, reveal any enalapril or other pharmaceutical liquid formulations having this stability or methods thereof. Because this stability element is not present in any of the cited references, the Office has not set forth a *prima facie* case of obviousness.

The Cited References Also Do Not Teach the Claimed Combination of Components in the Present Enalapril Formulations

As above, the claimed stable enalapril oral liquid formulation of claim 20 'consists essentially of' enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations and at a pH of less than about 3.5. As noted in the MPEP, "[t]he transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention. MPEP § 2111.03 (citing *In re Herz*, 537 F.2d 549, 551-52 (CCPA 1976) (emphasis in original)). While these claimed ingredients and excipients may individually be disclosed in the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, none of these references teach or suggest the claimed combination of only enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations and pH as stated in claim 20. Because these cited references alone or together do not teach or suggest this claimed

formulation, the Office has not set forth a *prima facie* case of obviousness for this additional reason.

B. The Office Fails to Provide a Reason to Arrive at the Enalapril Oral Liquid Formulation of the Instant Claims from the Cited References

The '747 Patent solely teaches enalapril powders with certain excipients and their reconstitution into liquids with stability at 12 weeks only

As the Office has pointed out, the '747 patent teaches enalapril powders with enalapril, mannitol and colloidal silicon dioxide that are for reconstitution by a syrup (e.g., Ora-Sweet). However, in contrast to the Office's assertion that the liquid preparations in the '747 patent are "stable for at least 36 wks at ambient or refrigerated conditions", Applicant respectfully points out the '747 patent does not teach that the reconstituted enalapril liquid is stable for at least 36 weeks, but rather stability of the reconstituted liquid at ambient temperatures was assessed only up to 12 weeks. See '747 patent, Example 6, col. 29, also reproduced below.

Enalapril Reconstituted Liquid - Ambient			
Time (Weeks)	Enalapril (%)	Endotoxin (%)	DOC (%)
0	97.2	0.43	0.04
2	96.8	0.75	0.08
4	96.9	0.87	0.08
8	95.4	1.35	0.12
12	93.7	2.22	0.17

As the '747 patent clearly shows, the reconstituted enalapril liquid formulation is stable for only 8 weeks and has unacceptable stability (less than 95% enalapril) at week 12. The '747 patent does not provide for, nor teach stability of enalapril liquid formulations for longer periods of time, much less stability for at least 12 months about 5±3 °C. Further, the '747 patent requires mannitol and colloidal silicon dioxide for stability and use of the disclosed enalapril powders, both of which are not required whatsoever in the present claims.

The '747 patent therefore fails to provide one of ordinary skill in the art any reason to attempt to make the claimed enalapril oral liquid formulations as this reference only describes

the preparation and use of enalapril powders for reconstitution. The '747 patent does not teach or suggest modifying or improving these enalapril powders into a ready-to-use enalapril liquid formulation that is stable for 12 months. Furthermore, one of ordinary skill in the art would be led by the '747 patent to include mannitol and colloidal silicon dioxide due to their important functions for powder formulations, which is not needed nor contemplated in the enalapril liquid formulations of the present claims.

Nahata only teaches the extemporaneous preparation of oral enalapril suspensions from grinding commercially available tablets and fails to provide a reason for modification of these preparations

As mentioned previously, Nahata describes in detail the process of grinding the enalapril tablets, mixing with certain suspending and syrup liquid vehicles to form a resultant oral suspension. While Nahata teaches enalapril oral suspensions from ground enalapril tablets, nothing in Nahata provides any reason or rationale of how one of ordinary skill in the art would use these teachings to arrive at the claimed stable enalapril oral liquid formulations, let alone pharmaceutical enalapril oral liquid formulations with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations and at a pH of less than about 3.5. In fact, Nahata does not even teach, disclose or suggest the preparation of any enalapril oral liquid formulations whatsoever as an alternative to the extemporaneous preparation method.

Further, Applicant respectfully points out that one skilled in the art would not use Nahata to arrive at the claimed enalapril oral liquid formulations. As the Office is no doubt aware, the crushing or grinding of tablets to form oral suspensions has many issues including stability, solubility, uniformity, etc. Indeed, the Mosher Declaration states that when compounding extemporaneous preparations, “[t]here is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid thus leading to potential dosing errors” and that “there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar.” See Mosher Declaration, ¶ 12.

Nahata therefore fails to provide one of ordinary skill in the art any reason to attempt to make the claimed enalapril oral liquid formulations as this reference only describes extemporaneously making oral liquid suspensions from enalapril tablets. Nahata does not teach

or suggest modifying or improving these oral liquid suspensions by adding or changing excipients. In forming new enalapril oral liquid formulations that exhibit the stability and homogeneity properties recited in the instant claims, one of ordinary skill in the art would not select Nahata by virtue of its teaching in the use of enalapril tablets as a starting material.

Bicitra, Ora-sweet, and Rippley also fail to provide a reason to arrive at the claimed enalapril liquid formulation alone or in combination with the '747 Patent and/or Nahata

The Bicitra and Ora-sweet references describe commonly used excipients: a citric acid buffering solution and syrup for extemporaneous or reconstituted preparations respectively. Applicant does not disagree nor dispute their various teachings. However, Applicant respectfully points out that neither Bicitra nor Ora-sweet provide any reason to make a stable enalapril liquid formulation alone or in combination with the '747 Patent and/or Nahata.

Further, Rippley is cited for its teaching of using a Bicitra solution in its extemporaneous preparations from enalapril tablets, however the reference itself provides no stability data whatsoever.

Accordingly, the Office has not demonstrated a reason or rationale for arriving at the claimed enalapril liquid compositions of the present application based on the disclosures in the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley.

C. The Combination of the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley Provide No Reasonable Expectation of Success of the Claimed Subject Matter

The second measure of obviousness requires that the combination of elements would have yielded "predictable results" *i.e.*, whether there would have been a reasonable expectation of success. To have a reasonable expectation of success, "one must be motivated to do more than merely "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful."

Medichem, S.A. v. Robaldo, 327 F.3d 1157, 1165 (Fed. Cir. 2006).

At the outset, Applicant respectfully points out that the Office is combining five disparate references to arrive at the claimed enalapril formulations of the present application. The '747

patent is directed to enalapril powders for reconstitution, Nahata and Rippley are directed to extemporaneous oral suspensions based on grinding enalapril tablets, and Ora-Sweet and Bicitra are descriptions of commonly used pharmaceutical excipients. While elements of the instant claims can be found scattered throughout these different references, there is no context or disclosure which brings forth these elements to the forefront and allows one to combine them successfully. Instead each reference discloses many other excipients that could potentially be used in equal measure.

The enalapril tablets used in the extemporaneous preparations of Nahata contain, in addition to enalapril, lactose, magnesium stearate, sodium bicarbonate, starch, and iron oxide. Ora-Plus is an oral suspending vehicle that has a pH of approximately 4.2 and that contains purified water, microcrystalline cellulose, sodium carboxymethylcellulose, xanthan gum, carrageenan, buffering agents (trisodium phosphate and citric acid), an antifoaming agent (simethicone), and preservatives (potassium sorbate and methylparaben). Ora-Sweet syrup vehicle is a flavoring vehicle that is buffered to a pH of approximately 4.2 and that contains purified water, sucrose, glycerin, sorbitol (5%), flavoring, buffering agents (sodium phosphate and citric acid), and preservatives (potassium sorbate and methylparaben). Nahata therefore teaches that these extemporaneously prepared suspensions from enalapril tablets contain a myriad of components, the majority of which are not present in the claimed formulations of the '603 application.

Similarly, the reconstituted enalapril formulations of the '747 patent contain, in addition to enalapril, mannitol, colloidal silicon dioxide and the Ora-Sweet syrup which also contains water, sucrose, glycerin, sorbitol (5%), flavoring, buffering agents (sodium phosphate and citric acid), and preservatives (potassium sorbate and methylparaben) as discussed above.

The following table lists the components that are present in the Nahata and the '747 patent formulations in comparison with the stable enalapril liquid formulation of the present claims:

Enalapril Extemporaneous Formulation (Ora-Sweet/Ora-Plus)	Enalapril Powder for Reconstitution Formulation	Formulation of Present Claims
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Enalapril Extemporaneous Formulation (Ora-Sweet/Ora-Plus)	Enalapril Powder for Reconstitution Formulation	Formulation of Present Claims
Enalapril	enalapril	enalapril
lactose	mannitol	sucralose
magnesium stearate	colloidal silicon dioxide	citric acid
sodium bicarbonate	sucrose	sodium citrate dihydrate
starch	glycerin	sodium benzoate
iron oxide	sorbitol	water
microcrystalline cellulose	flavoring	
carboxymethylcellulose sodium	citric acid	
xanthan gum	sodium phosphate	
carrageenan	methylparaben	
calcium sulphate	potassium sorbate	
trisodium phosphate	water	
citric acid		
dimethicone		
potassium sorbate		
methylparaben		
flavoring		
sorbitol		
glycerin		
sucrose		
water		

As apparent, the extemporaneously prepared formulation from Nahata contains 19 components in addition to enalapril and water and the reconstituted formulation from the '747 patent contains 10 components in addition to enalapril and water. In contrast, the formulation of the present claims has only four ingredients along with enalapril and water. Moreover, these additional excipients in the other formulations are not needed or contemplated in the claimed enalapril liquid formulations as none of them are needed or necessary to produce an oral enalapril liquid formulation of the present claims that is stable and homogeneous for at least 12 months at 5±3 °C.

In addition, there is no guidance whatsoever to keep or eliminate the components if one were to use Nahata or the '747 patent as a starting point to arrive at the claimed enalapril liquid formulations. When the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley are combined, one ordinarily skilled in the art is merely taught that any one of the many of excipients disclosed in

these references may potentially be combined with the extemporaneous enalapril formulations of Nahata and/or the reconstituted enalapril formulations of the '747 patent. As such, the prior art does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations, much less any expectation that the combination of with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations and at a pH of less than about 3.5 would be successful in forming a stable enalapril liquid formulation. One would need to consider all of these excipients and, through trial-and-error, determine whether each and every one of these components was necessary for stability or if they could be varied or eliminated. Simply put, to arrive at the combination of these specific components using the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, one skilled in the art must "vary all parameters or try each of the numerous possible choices" of the references without "direction as to which of the many choices is likely to be successful." *Medichem*, 437 F.3d at 1165. This is precisely what courts have held not to be a reasonable expectation of success. *Id.*; *see also, In re O'Farrell*, 853 F.3d 894, 903-4,

Since a reasonable expectation of success cannot be derived from the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, Applicant respectfully submits that the Office is improperly relying on the prior art disclosures as a basis for finding reasonable expectation of success and is using a hindsight reconstruction analysis to arrive at the present claims.

Accordingly, because the Office has not demonstrated a rationale for arriving at the claimed composition nor a reasonable expectation of success based on the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, the Office has failed to establish a *prima facie* case of obviousness. Applicant, therefore, respectfully requests that this rejection be withdrawn.

D. The Office must consider the secondary considerations of the claimed invention

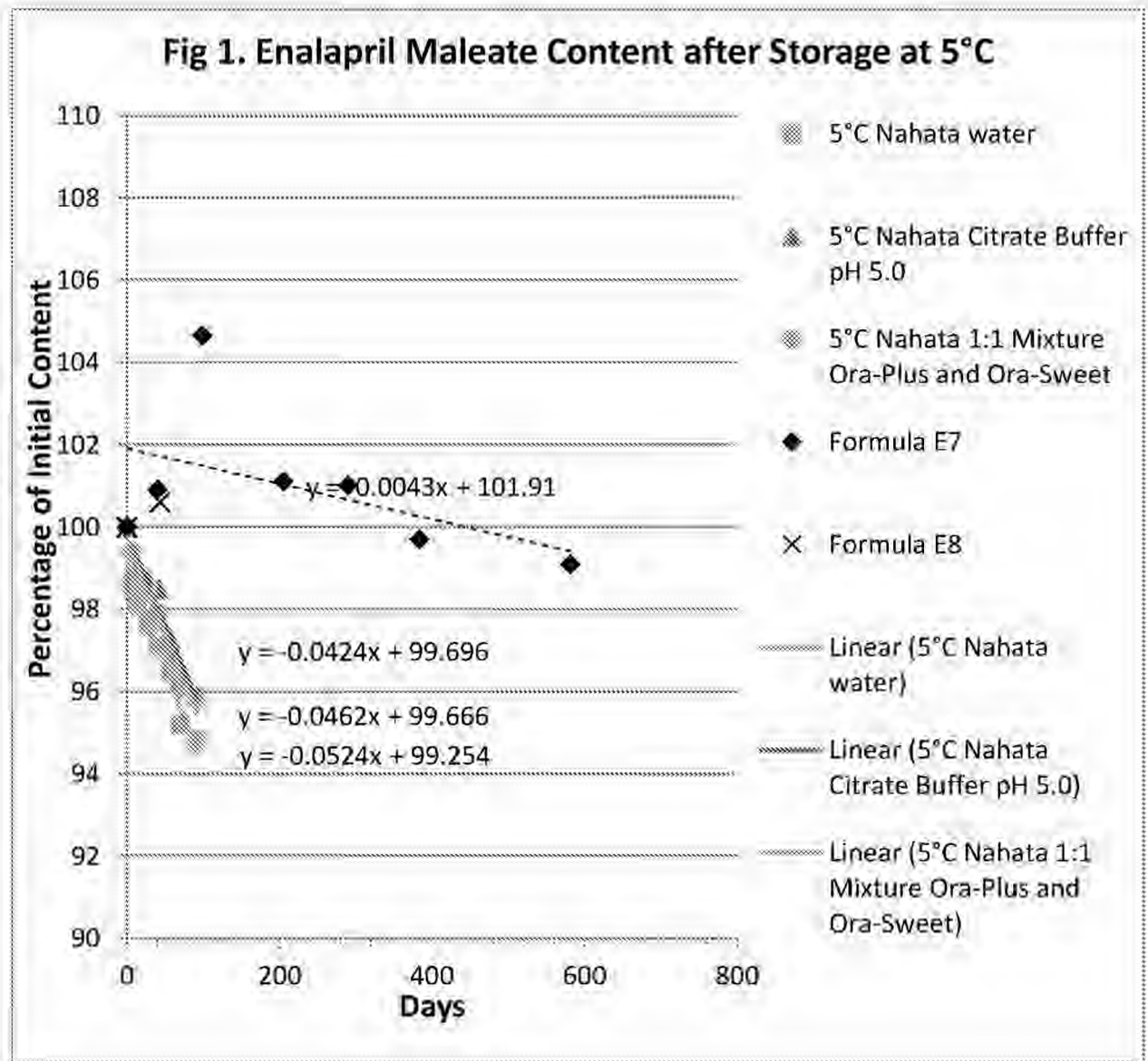
Finally, as well settled, presuming a *prima facie* case of obviousness were properly established, the Office is still required to consider all rebuttal evidence submitted by an Applicant. *See, e.g.,* MPEP §2145. This requirement remains unchanged following *KSR*, as the Federal Circuit has made clear. (*See In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007); MPEP §2145). In *In re Sullivan*, the Federal Circuit vacated and remanded a Board rejection of

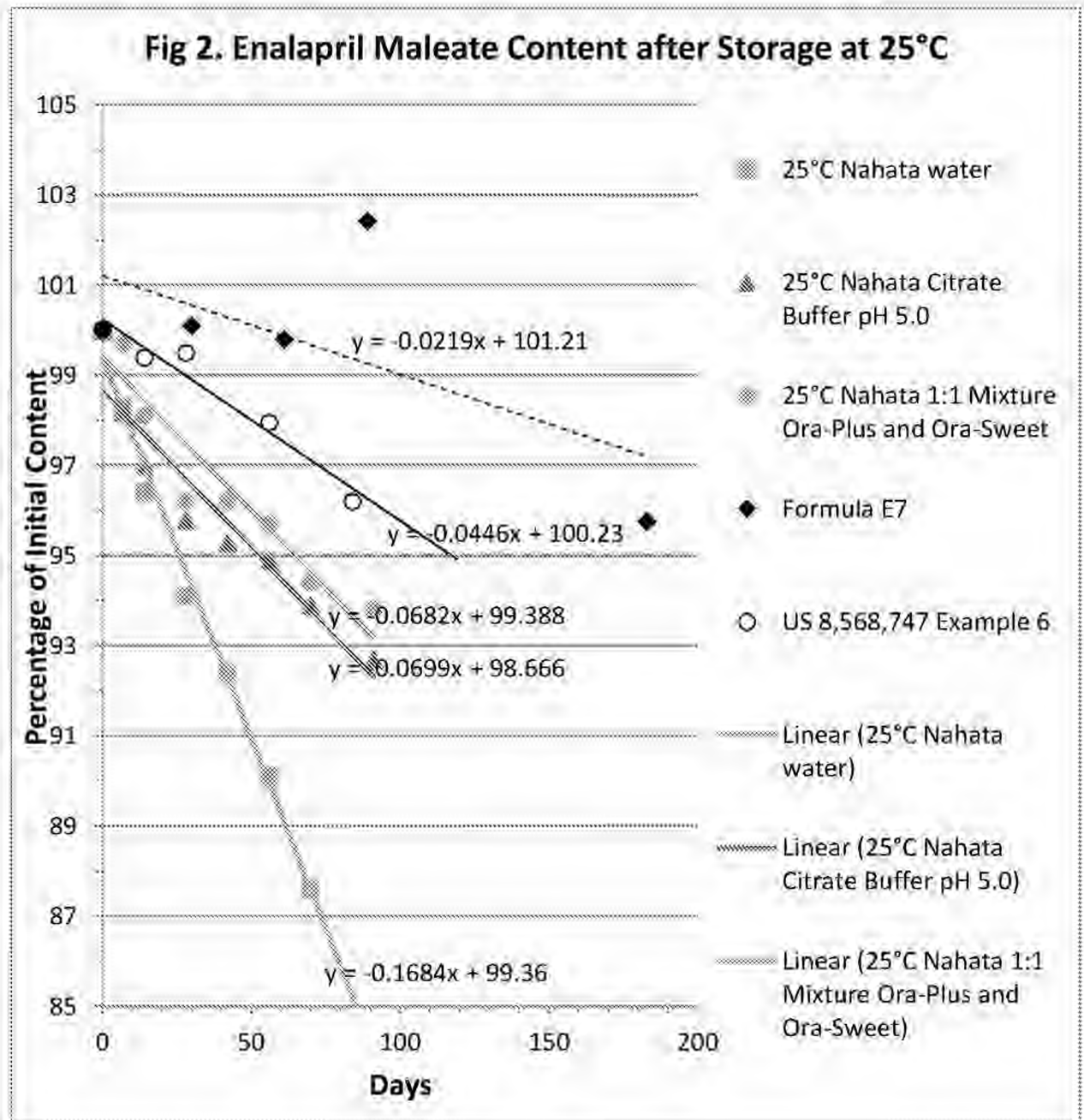
antivenom-composition claims because the Board failed to give any weight to the applicant's rebuttal evidence demonstrating that, *inter alia*, the combination of prior art elements exhibited unexpected efficacy while reducing the occurrence of adverse immune reactions in humans. (*Id.* at 1353). As the Court explained, "[w]hen a patent applicant puts forth rebuttal evidence, the Board must consider that evidence." (*Id.* at 1351).

Applicant submits that the present claims are not *prima facie* obvious over the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, as discussed above, and further submits that the subject matter in the claims have unexpected results with respect to stability of present enalapril liquid formulations.

Unexpected Results

As explained in the Mosher Declaration, the claimed stable enalapril liquid formulations are dramatically much more stable than the extemporaneous enalapril preparations of Nahata and the reconstituted enalapril formulations of the '747 patent. In the Mosher Declaration, Mosher plotted graphically, with linear regression of the data for extrapolation of the stability data published by Nahata et al. and the '747 patent, as well as corresponding E7 and E8 enalapril formulations, which are similar to or within the instant claims.





As evidenced by the above graphs, the E7 formulation demonstrates no loss of enalapril for at least 12 months at 5 °C and about 100 days at 25 °C. The E8 formulation, which has only one data point, is expected to trend similarly. These results drastically contrast with the stability or lack thereof in the extemporaneous and reconstituted enalapril preparations where these cases, the enalapril degrades substantially after initial preparation. At about 90-100 days, the extemporaneous preparations are at about 95% of the starting enalapril concentration when

stored at either 4 °C or 25 °C and the reconstituted formulation degrades after 8 weeks at 25 °C. The unexpected stability results of the E7 and E8 formulations are not taught by Nahata or the '747 patent, and could not have been predicted or contemplated by the cited prior art. Nowhere does the prior art teach or suggest that a combination of enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations and at a pH of less than about 3.5 at the claimed concentrations would have resulted in such a dramatic stabilization of enalapril. Accordingly, Applicant has submitted evidence supporting the unexpected technical results achieved by the claimed stable enalapril liquid formulations which rebut any presumption of *prima facie* obviousness.

U.S. Patent Application No. 15/081,603

Attorney Docket No.: 43060-707.201

CONCLUSION

Applicant submits that this response fully addresses the Office Action mailed January 17, 2017. Applicant believes that for the reasons set forth herein, the pending claims are in condition for allowance and early and favorable consideration is respectfully requested.

In the event that any fees are required in connection with this submission, the Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 43060-707.201).

Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858) 350-2318.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: February 3, 2017

By: /Clark Lin /
Clark Y. Lin, Ph.D., Esq.
Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2306
Customer No. 021971

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Examiner: Stephanie K. Springer
Serial No.: 15/081,603	Confirmation No.: 3892
Filed: March 25, 2016	Customer No.: 021971
Title: ENALAPRIL FORMULATIONS	

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132

I, **Gerold Mosher**, do hereby declare as follows:

1. I am currently employed at Silvergate Pharmaceuticals, Inc.
2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.
3. I have been employed at Silvergate Pharmaceuticals since 2013, as Vice President of Drug Development. As part of my job duties, I develop oral solutions for pediatric use. I have a small laboratory where I develop, characterize and move formulations through the steps required for FDA approval and eventual sale.
4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also

been employed by small startup companies to develop new solubilizing technology for oral, injectable and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for almost 38 years and have extensive experience in developing pharmaceutical formulations. My Curriculum Vitae is attached as Exhibit A.

6. I am familiar with the subject matter claimed in patent application 15/081,603, and am a named inventor on this application. Silvergate Pharmaceuticals is also the Assignee of the '603 application.

7. I am aware of the Non-Final Office Action mailed in this matter on January 17, 2017. I am also aware that the oral enalapril liquid formulation claims stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over US 8,568,747, Nahata et al. (Stability of Enalapril Maleate in three Extemporaneously Prepared Oral Liquids) ("Nahata"), Product Information of Bicitra (Sodium Citrate and Citric Acid Oral Solution) ("Bicitra"), Product Information of Ora-Sweet ("Ora-sweet"), and Rippley et al. (Pharmacokinetics Assessment of an Oral Enalapril Suspension for Use in Children) ("Rippley"). I have reviewed these cited references in the Non-Final Office Action.

8. I am submitting this declaration to address the comments made in the Office Action.

9. The '603 application relates to enalapril oral liquid formulations that are stable for least 12 months at 5 ± 3 °C. The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water at a pH of less than 3.5. Development of this described enalapril formulation was oriented on preparing a safe, stable, soluble oral liquid with minimal degradation and having acceptable taste for pediatric patients.

10. The currently approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in "Nahata" and subsequently administering the suspension to the

patient, or (3) reconstituting a powder in a liquid carrier, such as the described enalapril powder in US 8,568,747.

11. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty in swallowing oral dosage forms. For the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination. Similarly, reconstituting powders into a liquid carrier also requires an extra step and could introduce variability, solubility and contamination issues during the reconstitution.

12. As compared to these currently available methods, the enalapril oral liquid formulations claimed in the '603 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

13. It should be appreciated that the oral enalapril liquid formulations of the present claims are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

14. Evidence of this stability is found in exemplary formulations E7 and E8 which show minimal degradation as compared to current formulations. In this study, exemplary formulations E7 and E8 were stored at either refrigerated condition (5 °C) or at ambient condition (25 °C). Formulations details for E7 and E8 are as follows:

Composition of Enalapril Maleate Formulations		
Component	E7	E8
Enalapril maleate	1.00	1.00
Citric acid anhydrous	1.80	1.82
Sodium citrate anhydrous	0.16	0.15
Sodium benzoate	1.00	1.00
Sucralose	0.70	0.70
Mixed berry flavor	0.50	0.50
Water	qs	qs
pH (measured)	3.3	3.3

qs = sufficient quantity

15. In my review of the references cited in the Office Action, none of the references describe this stability of at least 12 months at 5±3 °C or any means of achieving this stability for enalapril formulations.

16. I have reviewed Nahata which describes the extemporaneous preparation of oral liquid enalapril formulations by crushing enalapril tablets with a mortar and pestle and suspending the resulting ground tablets in water, citrate buffer, or Ora-Plus/Ora-Sweet. On stability, Nahata states that the “compounded oral liquids [were] stable for 91 days at 4 and 25 °C” defining stable as “concentration after storage was ≥90% of the initial concentration. Table I of Nahata shows that the enalapril extemporaneous formulations exhibited about 5% loss of enalapril after about 56 days at 4 °C and about 5% loss of enalapril after about 91 days at 25 °C.

17. I have also reviewed US 8,568,747 which describes an oral liquid enalapril formulation obtained by reconstituting an enalapril powder in a liquid. The table in example 6 of US 8,568,747 shows that the resulting oral liquid formulation exhibited about 5% loss of enalapril after about 8 weeks at 25 °C.

18. I additionally reviewed Bicitra, Ora-sweet, and Rippley and they do not provide any stability of enalapril formulations whatsoever.

19. To compare the stability of the enalapril extemporaneous preparations as described in Nahata and the reconstituted liquid formulation of US 8,568,747, I submit the following data which depicts the enalapril content of formulations E7 at 5°C and 25 °C and E8 at 5 °C in Table A and Table B:

Table A: Enalapril content in formulations after storage at 5 °C¹

Days	Nahata			E7	E8
	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet		
0	100	100	100	100	100
7	98.6	98.7	99.4		
14	98.1	99.1	98.6		
28	97.6	98.7	98.4		
40				100.9	
42	97.1	98.5	97.9		100.3
56	96.5	97.3	96.9		
70	95.2	96.3	96.1		
91	94.8	95.9	95.8		
99				104.7	
205				101.1	
290				101.0	
383				99.7	
581				99.1	

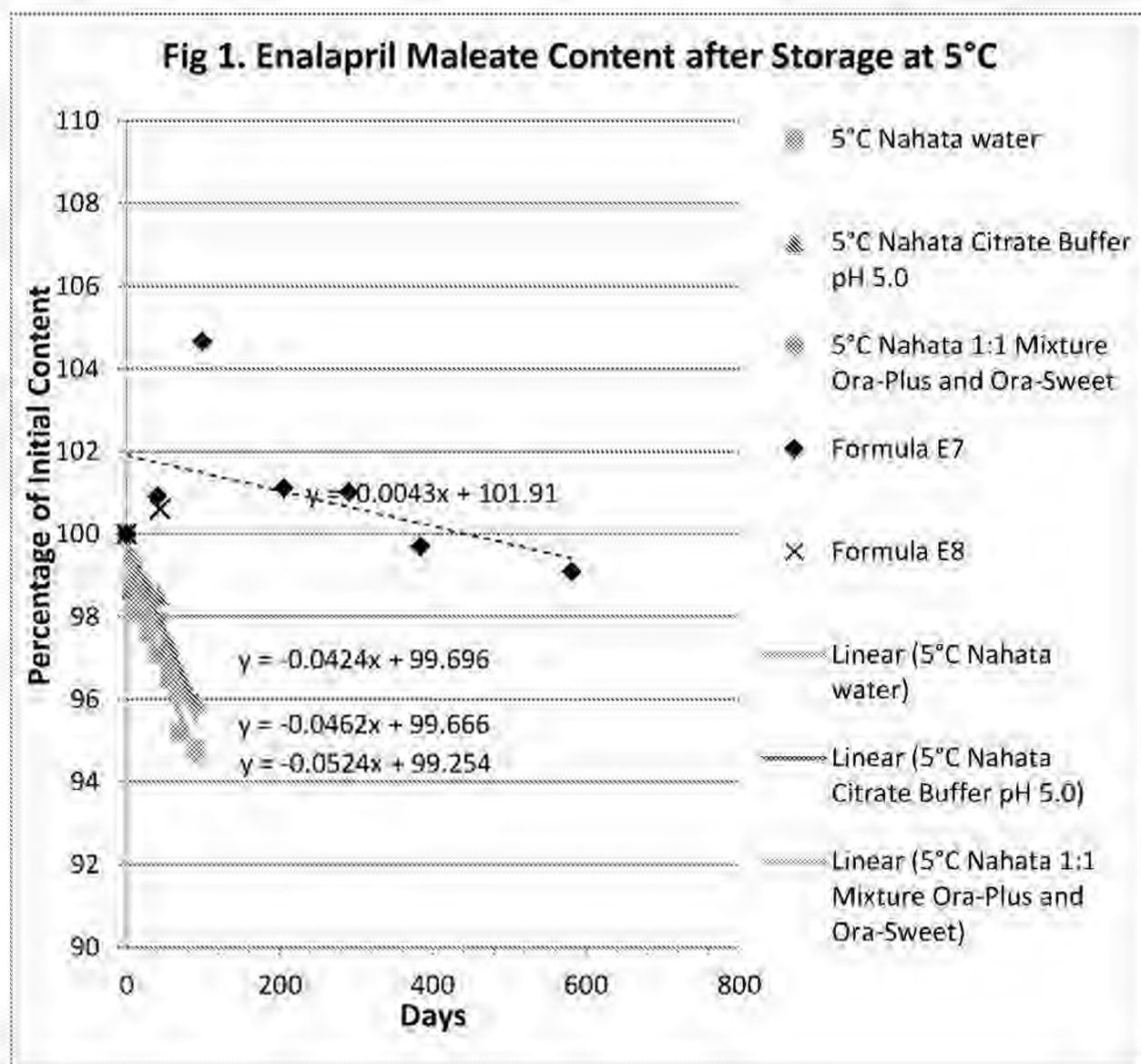
Table B: Enalapril content in formulations after storage at 25 °C

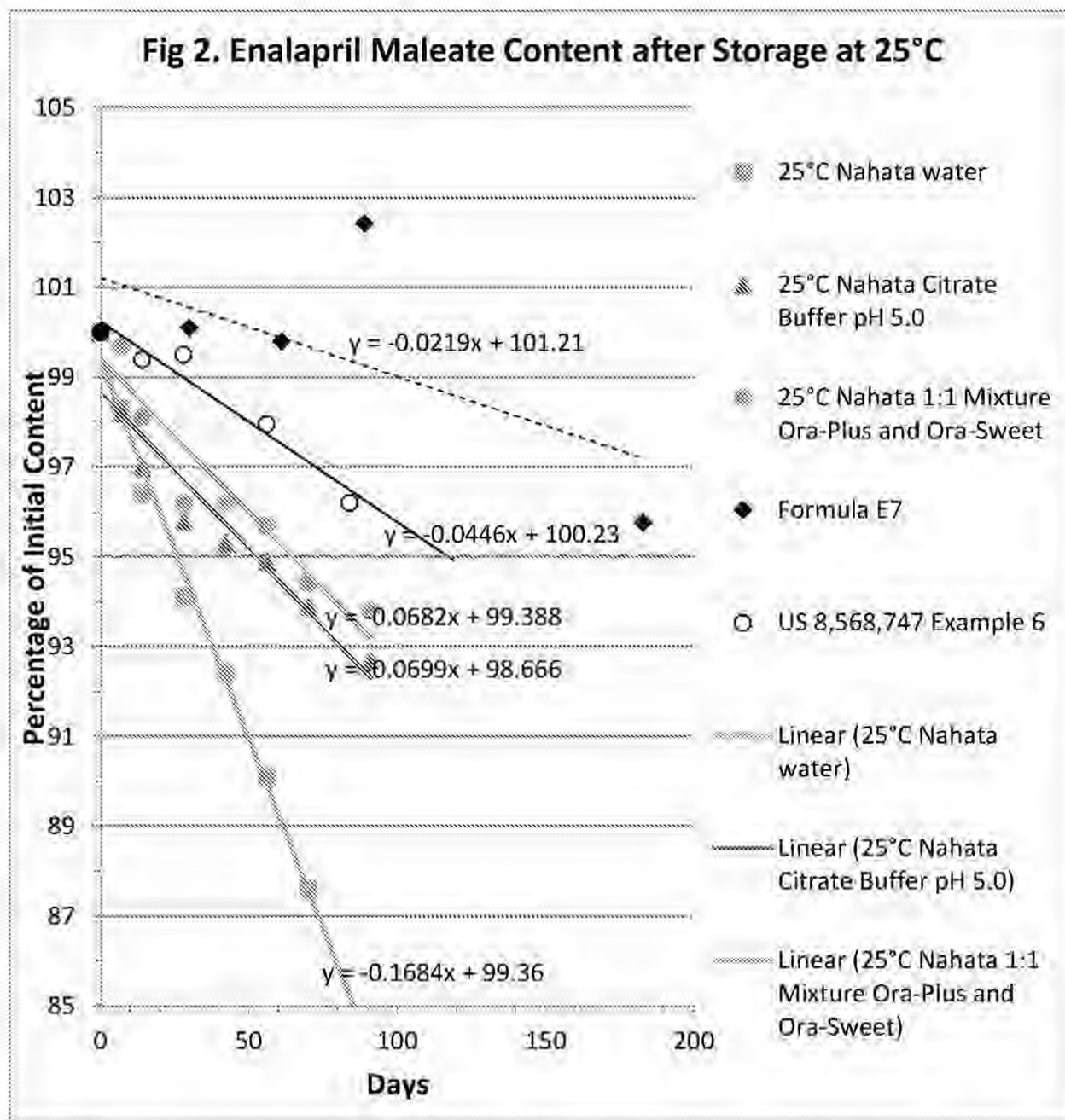
Days	Nahata			US 8,568,747	E7
	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	Example 6	
0	100	100	100	100	100
7	98.3	98.2	99.7		
14	96.4	97	98.1	99.4	
28	94.1	95.8	96.2	99.5	
30					100.1
42	92.4	95.3	96.2		
56	90.1	94.9	95.7	97.9	
61					99.8

¹ I note that US 8,568,747 does not provide stability data of the reconstituted liquid formulation at 5 °C.

70	87.6	93.9	94.4		
84				96.2	
89					102.4
91	84.1	92.7	93.8		
183					95.8

20. To further describe the contrast in stability, the enalapril concentrations published by Nahata, the US 8,568,747 enalapril concentrations, and the concentrations from E7 and E8 are plotted graphically (Fig. 1: 5 °C and Fig. 2: 25 °C) with linear regression of the data for extrapolation.





21. Table A and Fig. 1 show that E7 exhibits excellent stability for at least 18 months (581 days) at 5 °C with essentially no loss of enalapril content in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at 5 °C for more than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.

22. Table B and Fig. 2 show that E7 also exhibits better stability for at least 6 months (183 days) at 25 °C in contrast to the Nahata preparations and the reconstituted formulation of US 8,568,747.

23. The additional enalapril content data submitted for E7 and E8 shows that the formulations of the present application are significantly more stable, which in my opinion reflects the superior results and advantages, obtained with the oral liquid enalapril formulation of the present claims.

24. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under 18 U.S.C. 1001.

Respectfully submitted on this 2nd day of February, 2017



Gerold L. Mosher, Ph.D.

Curriculum Vitae**GEROLD L. MOSHER, Ph.D.****ADDRESSES**

Silvergate Pharmaceuticals, Inc.
 7300 West 110th Street, Suite 950
 Overland Park, KS 66210
 (913) 424-9294
 Jerry.mosher@silvergatepharma.com

Home
 12215 Avila Drive
 Kansas City, MO 64145
 Mobile (913) 424-9294
 jerry@coweemosher.com

EDUCATION

Ph.D., Pharmaceutical Chemistry (1986) University of Kansas, Lawrence, KS
 MS, Pharmaceutical Chemistry (1984) University of Kansas, Lawrence, KS
 BS, Pharmacy (1979) University of Kansas, Lawrence, KS

PROFESSIONAL EXPERIENCE

SILVERGATE PHARMACEUTICALS, INC (2013-Present)

Vice President of Drug Development

VERROW PHARMACEUTICALS, INC., Lenexa, KS (2008-present)

Scientific Advisor (2013-present)

Chief Scientific Officer and Vice President of Product Development (2008-2013)

CYDEX PHARMACEUTICALS, INC., Overland Park, KS (1998-2008)

Sr. Director, Product Development

UNIVERSITY OF MISSOURI-KANSAS CITY, Kansas City, MO (1996-1998)

Research Associate Professor, Division of Pharmaceutical Science (1996-1998)

Associate Director of the Center for Pharmaceutical Technology (1996-1998)

MIDWEST RESEARCH INSTITUTE, Kansas City, MO (1995-1996)

Manager, Pharmaceutical Product Development Section (1996)

Senior Chemist, Formulations Group Leader (1995)

INTERX DIVISION OF MERCK & COMPANY, Lawrence, KS (1992-1995)

Research Fellow

ELI LILLY & COMPANY, Indianapolis, IN (1986-1992)

Research Scientist (1990-1992)

Senior Pharmaceutical Chemist (1986-1990)

ST. JOSEPH HOSPITAL, Concordia, Kansas (1979-1981)

Staff Pharmacist

MEMBERSHIPS

American Association of Pharmaceutical Scientists (AAPS)

Phi Lambda Upsilon Honorary Chemical Society

Sigma Xi

PATENTS (US only)

GL Mosher and DW Miles, Unpublished patent application, filed 2015, Patent Pending

GL Mosher and DW Miles, Unpublished patent application, filed 2015, Patent Pending

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use, Publication 2016/0058786, Patent Pending.

JD Pipkin, GL Mosher and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof, Publication 2015/0050355, Patent Pending.

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. US Patent 9,125,945 (2015).

GL Mosher, SG Machatha and DJ Cushing, Pharmaceutical Compositions Comprising Prasugrel and Cyclodextrin Derivatives and Methods of Making and Using the Same. Publication 2015/0005341, Patent Pending.

GL Mosher, Stabilized Formulation Containing Iodinated Contrast Agents and Cyclodextrins. Publication 2014/0377185, Patent Pending.

GL Mosher, Stabilized Formulation Containing Iodinated Contrast Agents and Cyclodextrins. Publication 2013/0323181, Patent Pending.

JD Pipkin, RO Zimmerer, DO Thompson and GL Mosher, Inhalant Formulation Containing Sulfoalkyl Ether Cyclodextrin and Corticosteroid. Publication 2013/0303498, Patent Pending.

JD Pipkin, RO Zimmerer, DO Thompson and GL Mosher, Inhalant Formulation Containing Sulfoalkyl Ether Cyclodextrin and Corticosteroid. Publication 2013/0059826, Patent Pending.

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. US Patent 8,853,236 (2014).

GL Mosher, JD Pipkin and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 8,846,901 (2014).

GL Mosher, SG Machatha and DJ Cushing, Pharmaceutical Compositions Comprising Prasugrel and Cyclodextrin Derivatives and Methods of Making and Using the Same. US Patent 8,835,407 (2014).

JD Pipkin, GL Mosher and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 8,829,182 (2014).

JD Pipkin, GL Mosher and DB Hecker, DPI Formulation Containing Sulfoalkyl Ether Cyclodextrin. Publication 2013/0197105, Patent Pending.

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. US Patent 8,343,995 (2013).

JD Pipkin, GL Mosher and DB Hecker, DPI Formulation Containing Sulfoalkyl Ether Cyclodextrin. Publication 2012/0164184, Patent Pending.

GL Mosher, SG Machatha and DJ Cushing, Pharmaceutical Compositions Comprising Prasugrel and Cyclodextrin Derivatives and Methods of Making and Using the Same. US Patent 8,236,782 (2012).

JD Pipkin, GL Mosher and DB Hecker, DPI Formulation Containing Sulfoalkyl Ether Cyclodextrin. US Patent 8,114,438 (2012).

GL Mosher, JD Pipkin and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 8,049,003 (2011).

JD Pipkin, GL Mosher and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 7,629,331 (2009).

DO Thompson and GL Mosher, Formulations Containing Propofol and a Sulfoalkyl Ether Cyclodextrin. US Patent 7,034,013 (2006).

GL Mosher, KT Johnson, AA Gayed, and DO Thompson, Formulations Containing Amiodarone and a Sulfoalkyl Ether Cyclodextrin. US Patent 6,869,939 (2005).

VJ Stella, RA Rajewski, MR Venkatramana, JW McGinity, and GL Mosher, Sulfoalkyl Ether

Cyclodextrin Based Controlled Release Solid Pharmaceutical Formulations. US Patent 6,046,177 (2000).

GL Mosher. Absorption Enhancer/Solubilizer Combination for Improved Bioavailability of a Zwitterionic Compound. US Patent 5,525,596 (1996).

GL Mosher and MV Mullen. R-Forms of Cefuroxime Axetil. US Patent 5,063,224 (1991).

PUBLICATIONS

Elizabeth S. Rowe, Vernon D. Rowe, Sangita Biswas, Gerold Mosher, Lovella Insisiennay, Marlies K. Ozias, Michael R. Gralinski, John Hunter, James S. Barnett, (2016) Preclinical Studies of Kidney Safe Iodinated Contrast Agent, *J. Neuroimaging*, May 12, 2016 online.

D Cushing, P Souney, W Cooper, G Mosher, M Adams, S Machatha, B Zhang, and P Kowey. Assessment of the pharmacokinetics and platelet aggregation inhibitory effects of a novel intravenous formulation of clopidogrel in humans, *Clin. Exp. Pharm. Physiol.*, 39: 3-8 (2012).

GL Mosher, VD Antle, and JD Pipkin, Sulfobutylether β -Cyclodextrin, in Handbook of Pharmaceutical Excipients, 7th Edition by Rowe, R.C., Sheskey, P.J., Cook, W.G., and Fenton, M.E., Eds, London: Pharmaceutical Press, 823-826 (2012).

GL Mosher and SG Machatha, Complexation: Cyclodextrins, in Encyclopedia of Pharmaceutical Science and Technology, 4th Edition by Swarbrick, J., New York: Informa Healthcare USA Inc., (2013).

GL Mosher and JD Pipkin, Sulfobutyl Ether β -Cyclodextrin, in Handbook of Pharmaceutical Excipients, 6th Edition by Rowe, R.C., Sheskey, P.J. and Quinn, M.E, Eds, London: Pharmaceutical Press, 714-717 (2009).

GL Mosher and JD Pipkin, Sulfobutyl Ether β -Cyclodextrin, in Handbook of Pharmaceutical Excipients, 5th Edition by Rowe, R.C., Sheskey, P.J. and Owen S.C, Eds, London: Pharmaceutical Press, 754-757 (2006).

G Mosher and DO Thompson, Complexation: Cyclodextrins, in Encyclopedia of Pharmaceutical Technology: Third Edition by Swarbrick, J., New York: Informa Healthcare USA Inc., Volume 2, 671-696 (2006).

GL Mosher and JD Pipkin, Sulfobutyl Ether β -Cyclodextrin, in Pharmaceutical Excipients 2004 by Rowe, R.C., Sheskey, P.J. and Owen S.C, Eds, London: Pharmaceutical Press (2004).

SF Lockwood, S O'Malley and GL Mosher, Improved aqueous solubility of crystalline astaxanthin (3,3'-dihydroxy- β , β -carotene-4,4'-dione) by Captisol[®] (sulfobutyl ether β -cyclodextrin), *J. Pharm. Sci.*, 92(4): 922-926 (2003).

GL Mosher and DO Thompson, Complexation and Cyclodextrins, in Encyclopedia of Pharmaceutical Technology by Swarbrick, J. and Boylan, J.C., New York: Marcel Dekker, Inc., Volume 19, 49-88 (2000).

GL Mosher, The determination of interfacial transfer constants using side-by-side diffusion cells, *Pharm. Res.*, 11(9): 1325-1329 (1994).

GL Mosher, J McBee and DB Shaw, Esterase activity towards the diastereomers of cefuroxime axetil in the rat and dog, *Pharm. Res.*, 19(5): 687-689 (1992).

GL Mosher and J McBee, Photoreactivity of LY277359 maleate, a 5-HT₃ receptor antagonist, in solution, *Pharm. Res.*, 8(10): 1215-1222 (1991).

GL Mosher, H Bundgaard, E Falch, C Larsen, and T Mikkelsen, Ocular bioavailability of pilocarpic acid mono- and diester prodrugs as assessed by miotic activity in the rabbit, *Int. J. Pharm.*, 39: 113-120 (1987).

H Bundgaard, E Falch, C Larsen, GL Mosher and T Mikkelsen. Pilocarpine prodrugs. II. Synthesis, stability, bioconversion, and physicochemical properties of sequentially labile pilocarpic acid diesters, J. Pharm. Sci., 75: 775-783 (1986).

GL Mosher, Theoretical and Experimental Evaluation of Pilocarpine Prodrugs for Ocular Delivery, Dissertation for Doctor of Philosophy, (1986).

GL Mosher, Diethylpropion, a monograph in Chemical Stability of Pharmaceuticals by Connors, Amidon, Kannon and Stella, 2nd Edition, New York, John Wiley and Sons, (1986).

H Bundgaard, E Falch, C Larsen GL Mosher and T Mikkelsen, Pilocarpic acid esters as novel sequentially labile pilocarpine prodrugs for improved ocular delivery, J. Med. Chem., 28: 979-781 (1985).

GL Mosher and TJ Mikkelsen, Permeability of the n-alkyl p-aminobenzoate esters across the isolated corneal membrane of the rabbit, Int. J. Pharm., 2: 239 (1979).

ABSTRACTS/PRESENTATIONS

S Biswas, ES Rowe, G Mosher, MK Ozias, MR Gralinski, and VD Rowe, Veropaque, A Novel Contrast Formulation, Mitigates Contrast Induced Acute Kidney Injury, 24th Annual Transcatheter Cardiovascular Therapeutics Meeting, Miami, FL (Nov 22-26, 2012). Abstract in J Am Coll Cardiol 60(17) Suppl. B :B40 (2012).

JD Pipkin, SG Machatha, GL Mosher, and Q He, Bioequivalence of a Captisol-Enabled[®] fosphenytoin sodium injection formulation to the marketed reference listed product via IV and IM administration in healthy volunteers, 64th Annual Meeting of the American Epilepsy Society, San Antonio, TX (Dec 3-7, 2010).

SG Machatha, C Fulk, GL Mosher and JD Pipkin, The effects of Captisol[®] on the solubilization and stabilization of antiepileptic drugs, 2010 AAPS Annual Meeting and Exposition, New Orleans, LA (Nov 14-18, 2010).

S Biswas, ES Rowe, G Mosher, L Tejada, MK Ozias, and VD Rowe, Nephroprotective effects of substituted cyclodextrins, 15th International Cyclodextrin Symposium, Vienna Austria, (May 9-12, 2010).

SG Machatha, GL Mosher and DJ Cushing, Effects of modified cyclodextrin derivatives on the solubility and stability of prasugrel in aqueous formulations, 2009 AAPS Annual Meeting and Exposition, Los Angeles, CA (Nov 8-12, 2009).

PF Souney, J Cowee, DJ Cushing, G Mosher, and P Holmes, Stability of a cyclodextrin-based IV formulation of amiodarone when diluted with 5 percent dextrose or 0.9 percent sodium chloride injections in both PVC and polyolefin intravenous bags over 7 days, 2009 ASHP Summer Meeting, Rosemont, IL (June 14-17, 2009).

D Cushing, R Lipicky, P Kowey, C Cannon, M Adams, W Cooper and G Mosher, Assessment of the pharmacokinetic and pharmacodynamic effects of intravenous clopidogrel in humans, American College of Cardiology 58th Annual Scientific Session, Orlando, FL (Mar 28-31, 2009).

PF Souney, J Cowee, G Mosher and DJ Cushing, Stability of intravenous amiodarone formulations in glass, polyolefin and polyvinylchloride containers over 72 hours, ASHP Midyear Clinical Meeting, Orlando, FL (Dec 7-11, 2008).

SG Machatha, RL Wedel, KT Johnson and GL Mosher, Effects of modified cyclodextrin derivatives on the solubility and stability of clopidogrel bisulfate in aqueous formulations, 2007 AAPS Annual Meeting and Exposition, San Diego, CA (Nov 10-15, 2007).

PW Holmes, SG Machatha, CF Fulk and GL Mosher, The common ion effect and its impact on the development of a stable Captisol-Enabled[®] fosphenytoin sodium injection formulation, 2007 AAPS

Annual Meeting and Exposition, San Diego, CA (Nov 10-15, 2007).

DJ Cushing, WD Cooper, GL Mosher, MR Gralinski and BW Massey. Pharmacokinetic and pharmacodynamic effects of a novel intravenous formulation of clopidogrel bisulfate, 2007 AAPS Annual Meeting and Exposition, San Diego, CA (Nov 10-15, 2007).

G Mosher, Clinical pharmacokinetics and taste assessment comparison of an aqueous sulfobutylether- β -cyclodextrin based oral formulation of sertraline HCl to Zoloft oral concentrate, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

KT Johnson and G Mosher, Investigation of atypical bi-phasic complexation curves observed when charged cyclodextrins solubilize charged drug compounds, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

R Wedel, A Gayed and GL Mosher, Development of an aqueous-based oral solution formulation of sertraline HCl using sulfobutylether- β -cyclodextrin, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

CF Fulk, A Gayed, B Lund, GL Mosher, DO Thompson and R Wedel, Preserved formulations containing Captisol[®] brand of sulfobutylether- β -cyclodextrin, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

SJ Carter, DA Robaugh, RO Zimmerer, GL Mosher and NJ Cogburn, Overcoming unique challenges in developing a method for the quantitation of sulfobutyl ether β -cyclodextrin in rat and dog plasma by LC/MS, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

S Katpally, MK Ghorab, D Thompson, G Mosher, JD Madura and MC Adeyeye, Characterization of bile salt / SBE7- β -cyclodextrin interactions using isothermal titration calorimetry, 2002 AAPS Annual Meeting and Exposition, Montreal Canada (Nov 10-14, 2002).

ML Sima, CF Fulk, and GL Mosher, Captisol-Enabled[™] Propofol: Formulation approaches to reduce oxidation, 2002 AAPS Annual Meeting and Exposition, Montreal Canada (Nov 10-14, 2002).

A Vargas-Perex, S Katpally, A Jain, G Mosher, D Thompson and MC Adeyeye, Complexation characteristics of sulfobutylether 7- β -cyclodextrin (SBE7-CD) with chenodeoxycholic acid, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

S Katpally, A Vargas-Perez, D Thompson, G Mosher and MC Adeyeye, Complexation characteristics of sulfobutylether- β -cyclodextrin (SBE7-CD) with bile acids, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

KT Johnson and G Mosher, Development and qualification of a fluorescence method for the determination of sulfobutylether-7- β -cyclodextrin delivered in an aerosol inhalation safety study, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

G Mosher, and C Fulk, Co-solvent effects on the rate and extent of solubilization of drugs by Captisol[®] brand of sulfobutyl ether β -cyclodextrin, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

CA Vasquez, NA Neilan and GL Mosher, In vitro evaluation of biocompatibility of a dose formulation, 40th Annual Meeting of the Society of Toxicology, San Francisco, CA, (Mar 25-29, 2001).

C Fulk, SM Ghate, GL Mosher and DO Thompson, Preparation of the ammonium salt of sulfobutyl ether β -cyclodextrin (Captisol[®]) for use in controlled release formulations, 27th International Symposium on Controlled Release of Bioactive Materials, Paris, (July 7-13, 2000).

GL Mosher, Cyclodextrins, they're not just for breakfast any more, Kansas City Discussion Group of Pharmaceutical and Allied Scientists, (Jan 2000).

GL Mosher, S Bradley and E Evans, Continuous IV infusion studies in dogs, Kansas City Discussion Group of Pharmaceutical and Allied Scientists, (1996).

GL Mosher, K Trubitt-Johnson and RC Wood, Absorption enhancer solubilizer combination for improved bioavailability of a zwitterionic compound. 9th Annual AAPS National Meeting. (1994).

SA Sweetana and GL Mosher. Bile salt-insulin interactions. Optical spectroscopy studies. 6th Annual AAPS National Meeting. (1991).

J McBee and GL Mosher. Hydrolysis of four dihydrolysergic acid derivatives using in vitro enzyme systems from the rat and dog. 3rd Annual AAPS National Meeting. (1989).

GL Mosher and T Mikkelsen. An implicit method for modeling the simultaneous transport and metabolism of pilocarpine prodrugs across the excised rabbit cornea. Lilly Modeling Conference. (1987).

GL Mosher, H Bundgaard, E Falch and C Larsen. Effects of drug-protein binding on the precorneal loss of pilocarpine prodrugs. 1st Annual AAPS National Meeting. (1986).

GL Mosher, T Mikkelsen, H Bundgaard, E Falch and C Larsen. Prodrug-to-drug ocular bioconversion of pilocarpic acid diesters. 39th Annual APS Meeting. (1985).

GL Mosher, T Mikkelsen, H Bundgaard, E Falch and C Larsen. Pilocarpine prodrugs. II. Comparative miotic activities of pilocarpic acid esters in the rabbit following topical instillation. 37th Annual APS Meeting. (1984).

H Bundgaard, E Falch, C Larsen, GL Mosher and T Mikkelsen, S Pilocarpine prodrugs. I. Synthesis, physicochemical properties and kinetics of lactonization of pilocarpic acid esters. 37th Annual APS Meeting. (1984).

GL Mosher. Pharmacokinetics - principles and application. Pharmacy Continuing Education Fall Seminar Circuit. University of Kansas. (1984).

GL Mosher, T Mikkelsen and K Himmelstein. Diffusion of a series of homogenous compounds across single and laminated polymeric membranes. 15th Annual Graduate Student Pharmaceutical Research Meeting. (1983).

GL Mosher and T Mikkelsen. Corneal uptake of the n-alkyl p-aminobenzoate homologs. 27th Annual APS National Meeting. (1979).

GL Mosher and T Mikkelsen. Transport across the isolated corneal membrane and physicochemical drug properties. 125th Annual APhA National Meeting. Montreal, Canada (1978).



UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Feb 22 2017

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s) :
Clark Lin

S-signature:
/Clark Lin/

Registration Number:
67024

U.S. Application Number:
15081603

Confirmation Number:
3892

E-mail Address:
clin@wsgr.com

Phone Number:
8583502318

Proposed Time of Interview:
3-20-2017 11:00 AM ET

Preferred Interview Type:
In-person

I am the applicant or applicant's representative for this application:



UNITED STATES
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 3892
Serial No.: 15/081,603	Examiner: Stephanie K. Springer
Filed: March 03, 2016	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached response and all marked attachments are being deposited by Electronic Filing on March 22, 2017, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u>/Keiko A. Masuyama Hicks/</u> Keiko A. Masuyama Hicks</p>

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION
DATED JANUARY 17, 2017

Commissioner:

This is a supplemental amendment provided pursuant to an interview with the Office on March 20, 2017. This amendment supplements and incorporates the February 3rd response and amendments to the Office's January 17, 2017 Office Action. Applicant respectfully requests amendment of the patent application, and reconsideration and allowance of the pending claims.

Amendments to the Claims begins on page 2.

Remarks begin on page 5.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed.

Listing of the Claims:

1. (Currently Amended) A stable oral liquid formulation, comprising:
 - (i) about 1 mg/ml enalapril malate;
 - ~~(ii) about 0.70 mg/ml of a sweetener that is sucralose;~~
 - (ii) ~~(iii)~~ a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate;
 - (iii) ~~(iv)~~ about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) ~~(v)~~ water;
 wherein the pH of the formulation is less than about 3.5; and
 wherein the formulation is stable at about 5 ± 3 °C for at least 12 months;
 wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.
2. (Original) The formulation of claim 1, further comprising a flavoring agent.
3. (Cancelled).
4. (Original) The formulation of claim 1, wherein the pH is between about 3 and about 3.5.
5. (Original) The formulation of claim 4, wherein the pH is about 3.3.
6. (Original) The formulation of claim 1, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.
7. (Original) The formulation of claim 6, wherein the citrate concentration in the buffer is about 10 mM.
8. (Original) The formulation of claim 1, wherein the formulation is stable at about 5 ± 3 °C for at least 18 months.
9. (Original) The formulation of claim 1, wherein the formulation is stable at about 5 ± 3 °C for at least 24 months.

10. (Original) The formulation of claim 1, wherein the formulation does not contain
11. ~~(Original)~~ The formulation of claim 1, wherein the formulation does not contain silicon dioxide.
12. (Currently Amended) A stable oral liquid formulation, comprising:
 - (i) about 19.3 % (w/w of solids) enalapril maleate;
 - ~~(ii)~~ about 13.5 % (w/w of solids) of a sweetener that is sucralose;
 - (ii) ~~(iii)~~ a buffer comprising about 35.2 % (w/w of solids) citric acid and about 2.9 % (w/w of solids) sodium citrate dihydrate;
 - (iii) ~~(iv)~~ about 19.3 % (w/w of solids) of a preservative that is sodium benzoate; and
 - (iv) ~~(v)~~ water;
 wherein the pH of the formulation is less than about 3.5; and
 wherein the formulation is stable at about 5 ± 3 °C for at least 12 months;
 wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.
13. (Original) The formulation of claim 12, further comprising a flavoring agent.
14. (Cancelled).
15. (Original) The formulation of claim 12, wherein the pH is between about 3 and about 3.5.
16. (Original) The formulation of claim 15, wherein the pH is about 3.3.
17. (Original) The formulation of claim 12, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.
18. (Original) The formulation of claim 17, wherein the citrate concentration in the buffer is about 10 mM.
19. (Original) The formulation of claim 12, wherein the formulation is stable at about 5 ± 3 °C for at least 24 months.
20. (Previously Presented) A stable oral liquid formulation, consisting essentially of:
 - (i) about 1 mg/ml enalapril maleate;
 - (ii) about 0.70 mg/ml of a sweetener that is sucralose;
 - (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate;
 - (iv) about 1 mg/ml of a preservative that is sodium benzoate;

(v) a flavoring agent; and

(vi) water;

wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid if needed; and

wherein the formulation is stable at about 5 ± 3 °C for at least 12 months;

wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

21. (New) The stable oral liquid formulation of claim 1, further comprising about 0.70 mg/ml of a sweetener that is sucralose.

22. (New) The stable oral liquid formulation of claim 12, further comprising about 13.5 % (w/w of solids) of a sweetener that is sucralose.

REMARKS**Status of the Claims**

Claims 1 and 12 have been amended. Claims 21-22 have been added. Support for the new claims and the amendments is found at least in the original claims and throughout the specification. No new matter is presented by way of the amendments. Upon entry of the proposed amendment, claims 1-2, 4-13 and 15-22 will be under examination.

March 20 Applicant-Initiated Interview Summary

Applicant would like to extend thanks to Examiners Springer and Lundgren for a productive in-person interview on March 20, 2017 with Applicant's representative, Clark Lin and inventor, Gerold Mosher. Applicant and the Examiners discussed the enalapril formulation of the instant claims and its stability properties in comparison to those described in prior art references, Nahata, Rippley and the 8,568,747 patent. It is the Applicant's understanding that the Examiners appreciated the superior stability provided by the components and pH as recited in the claims. It is further Applicant's understanding that Examiner Lundgren suggested moving the sweetener, sucralose, from the independent claims to dependent claims. This reply and supplemental amendment submitted herewith adopts the Examiner's suggestion for the claim amendments.

U.S. Patent Application No.15/081,603

Attorney Docket No.: 43060-707.201

CONCLUSION

Applicant submits that this supplemental amendment pursuant to the interview dated March 20, 2017. Applicant believes that for the reasons set forth herein, the pending claims are in condition for allowance and early and favorable consideration is respectfully requested.

In the event that any fees are required in connection with this submission, the Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 43060-707.201).

Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858) 350-2318.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: March 22, 2017

By: /Clark Lin/

Clark Y. Lin, Ph.D., Esq.
Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2306
Customer No. 021971



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EXAMINER

SERINGER, STEPHANIE K

ART UNIT

PAPER NUMBER

1529

DATE MAILED: 04/19/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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15/081,603

03/25/2016

Gerold L. MOSHER

43060-707,201

3892

TITLE OF INVENTION: Enalapril Formulations

APPL. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
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nonprovisional

UNDISCOUNTED

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\$0

\$0

\$960

07/19/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

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I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

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If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/081,603	03/25/2016	Gerold L. MOSHER	43060-707.201	3892

TITLE OF INVENTION: Enalapril Formulations

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	07/19/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
SPRINGER, STEPHANIE K	1629	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

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Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

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5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/081,605	03/25/2016	Gerald L. MOSIER	43060-707,201	3892

21971 7590 04/19/2017
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER

SPRINGER, STEPHANIE K

ART UNIT PAPER NUMBER

1529

DATE MAILED: 04/19/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.** Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/081,603	Applicant(s) MOSHER ET AL	
	Examiner STEPHANIE SPRINGER	Art Unit 1629	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to Supplemental amendment filed 22 March 2017.
☐ A declaration(s)/affidavit(s) under 37 CFR 1.130(b) was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 1,2,4-13 and 15-22. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. <input type="checkbox"/> Notice of References Cited (PTO-892) 2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>2 pgs; 3 pgs</u> 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material 4. <input checked="" type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date <u>20 March 2017</u>	5. <input type="checkbox"/> Examiner's Amendment/Comment 6. <input type="checkbox"/> Examiner's Statement of Reasons for Allowance 7. <input type="checkbox"/> Other _____
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/STEPHANIE SPRINGER/ Examiner, Art Unit 1629	/JEFFREY S. LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629
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<i>Applicant-Initiated Interview Summary</i>	Application No.	Applicant(s)		
	15/081,603	MOSHER ET AL.		
	Examiner	Art Unit	AIA (First Inventor to File) Status	Page
	STEPHANIE SPRINGER	1629	Yes	1 of 2

All participants (applicant, applicant's representative, PTO personnel):

1. STEPHANIE SPRINGER (Examiner); Telephonic
2. Jeff Lundgren (SPE); In-Person
3. Clark Lin (Attorney); In-Person
4. Gerold Mosher (Inventor); In-Person

Date of Interview: 20 March 2017

Claim(s) discussed: 1, 12, 20

Identification of prior art discussed: '747, Rippley, Nahata

Amendment Proposed: Examiners suggested removing limitations directed towards the use of sucralose as the sweetener

Brief Description of main topic of discussion: Discussed claim amendments and declaration filed 3 February 2017.

Issues Discussed:

Item(s) under 35 U.S.C. 112:

Examiners agreed the claim amendments overcome the 112, 2nd rejection of record.

Item(s) under 35 U.S.C. 103:

It was mutually agreed that '747 is the closest prior art. The teachings of the prior art as a whole would not reasonably suggest that the instantly claimed composition would provide a stable solution at the recited pH over the recited timeframe.

		JEFFREY S. LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629
<p>Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable time limit of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.</p> <p>Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.</p> <p>Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicant's responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04</p> <p>Please further see:</p> <p>MPEP 713.04 Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b) 37 CFR § 1.2 Business to be transacted in writing.</p>		

U.S. Patent and Trademark Office

Application No. 15/081,603

Page 2 of 2

PTOL-413/413b (Rev. 01/01/2015)

Interview Summary

Paper No. 20170323

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** Mail Stop ISSUE FEE
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 or **Fax** (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 04/19/2017
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Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/081,603	03/25/2016	Gerold L. MOSHER	43060-707,201	3892

TITLE OF INVENTION: Enalapril Formulations

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	07/19/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
SPRINGER, STEPHANIE K	1629	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363):

- ☐ Change of correspondence address (or Change of Correspondence Address Form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
 (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Wilson Sonsini Goodrich & Rosati

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY AND STATE OR COUNTRY)

Silvergate Pharmaceuticals, Inc.

Greenwood Village, CO 80111

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 232415 (enclose an extra copy of this form)

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature

Clark LIN

Date

4/19/17

Typed or printed name Clark LIN

Registration No.

67024



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/081,603	06/06/2017	9669008	43060-707.201	3892

2197L 7290 05/17/2017

WILSON, SONSINI, GOODRICH & ROSATI
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 PALO ALTO, CA 94304-1050

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Gerold L. MOSIER, Kansas City, MO;
 Silvergate Pharmaceuticals, Inc., Greenwood Village, CO;
 David W. MILES, Kansas City, MO;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

PTO/AIA/15 (10-17)

Approved for use through 11/30/2020. OMB 0651-0032

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL <i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i>		Attorney Docket No. 43060-707.305	
		First Named Inventor Gerold L. MOSHER	
		Title ENALAPRIL FORMULATIONS	
		Priority Mail Express® Label No. Filed Electronically via EFS-Web on January 8, 2019	

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
<ol style="list-style-type: none"> 1. <input type="checkbox"/> Fee Transmittal Form (PTO/SB/17 or equivalent) 2. <input type="checkbox"/> Applicant asserts small entity status. <i>See 37 CFR 1.27</i> 3. <input type="checkbox"/> Applicant certifies micro entity status. <i>See 37 CFR 1.29.</i> <i>Applicant must attach form PTO/SB/15A or B or equivalent.</i> 4. <input checked="" type="checkbox"/> Specification [Total Pages <u>52</u>] <i>Both the claims and abstract must start on a new page.</i> <i>(See MPEP § 608.01(a) for information on the preferred arrangement)</i> 5. <input checked="" type="checkbox"/> Drawing(s) (35 U.S.C. 113) [Total Sheets <u>2</u>] 6. Inventor's Oath or Declaration [Total Pages <u>2</u>] <i>(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))</i> <ol style="list-style-type: none"> a. <input type="checkbox"/> Newly executed (original or copy) b. <input checked="" type="checkbox"/> A copy from a prior application (37 CFR 1.63(d)) 7. <input checked="" type="checkbox"/> Application Data Sheet * <i>See note below.</i> <i>See 37 CFR 1.76 (PTO/AIA/14 or equivalent)</i> 8. CD-ROM or CD-R <i>in duplicate, large table, or Computer Program (Appendix)</i> <div style="margin-left: 20px;"> <input type="checkbox"/> Landscape Table on CD </div> 9. Nucleotide and/or Amino Acid Sequence Submission <i>(if applicable, items a. – c. are required)</i> <ol style="list-style-type: none"> a. <input type="checkbox"/> Computer Readable Form (CRF) b. <input type="checkbox"/> Specification Sequence Listing on: <ol style="list-style-type: none"> i. <input type="checkbox"/> CD-ROM or CD-R (2 copies); or ii. <input type="checkbox"/> Paper c. <input type="checkbox"/> Statements verifying identity of above copies 	ACCOMPANYING APPLICATION PAPERS <ol style="list-style-type: none"> 10. <input type="checkbox"/> Assignment Papers (cover sheet & document(s)) Name of Assignee _____ 11. <input checked="" type="checkbox"/> 37 CFR 3.73(c) Statement <input checked="" type="checkbox"/> Power of Attorney <i>(when there is an assignee)</i> 12. <input type="checkbox"/> English Translation Document <i>(if applicable)</i> 13. <input type="checkbox"/> Information Disclosure Statement (PTO/SB/08 or PTO-1449) <div style="margin-left: 20px;"><input type="checkbox"/> Copies of citations attached</div> 14. <input type="checkbox"/> Preliminary Amendment 15. <input type="checkbox"/> Return Receipt Postcard <i>(MPEP § 503) (Should be specifically itemized)</i> 16. <input type="checkbox"/> Certified Copy of Priority Document(s) <i>(if foreign priority is claimed)</i> 17. <input type="checkbox"/> Nonpublication Request <i>Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.</i> 18. <input checked="" type="checkbox"/> Other: <u>Certification and Request for Prioritized Examination Under 37 CFR 1.102(e) - 1 pp.</u>

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
 (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS					
<input checked="" type="checkbox"/> The address associated with Customer Number: <u>21971</u> OR <input type="checkbox"/> Correspondence address below					
Name					
Address					
City	State	Zip Code			
Country	Telephone	Email			

Signature	/Clark Lin/	Date	January 8, 2019
Name (Print/Type)	Clark Y. Lin	Registration No. (Attorney/Agent)	67024

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

SLVGT-EPA_0104346

Doc Code: TRACK1.REQ

Document Description: TrackOne Request

PTO/AIA/424 (04-14)

**CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION
UNDER 37 CFR 1.102(e) (Page 1 of 1)**

First Named Inventor:	Gerold L. MOSHER	Nonprovisional Application Number (if known):	
Title of Invention:	ENALAPRIL FORMULATIONS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. ☒ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

- i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.
---OR---
(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.
- ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, or the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

- i. A request for continued examination has been filed with, or prior to, this form.
- ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
- iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
- iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
- v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature <u>/Clark Lin/</u>	Date <u>January 8, 2019</u>
Name (Print/Typed) <u>Clark Y. Lin</u>	Practitioner Registration Number <u>67024</u>

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.*

☒ *Total of 1 forms are submitted.

SLVGT-EPA_0104347

CLAIMS

WHAT IS CLAIMED IS:

1. A stable oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
2. The stable oral liquid formulation of claim 1 further comprising a sweetener.
3. The stable oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. The stable oral liquid formulation of claim 1 further comprising a flavoring agent.
5. The stable oral liquid formulation of claim 1, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, or a tartrate buffer.
6. The stable oral liquid formulation of claim 1, wherein the buffer comprises citric acid and sodium citrate.
7. The stable oral liquid formulation of claim 6, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.
8. The stable oral liquid formulation of claim 1, wherein the buffer comprises phosphoric acid and sodium phosphate.
9. The stable oral liquid formulation of claim 1, wherein the buffer concentration is about 5 mM to about 20 mM.
10. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH between about 3 and about 4.

11. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH at about 3.3.
12. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 18 months.
13. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 24 months.
14. A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
15. A stable oral liquid formulation, comprising:
 - (i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below;
 - (iii) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and
 - (iv) water;wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
16. The stable oral liquid formulation of claim 15 further comprising a sweetener.
17. The stable oral liquid formulation of claim 16, wherein the sweetener is sucralose.

18. The stable oral liquid formulation of claim 15 further comprising a flavoring agent.
19. The stable oral liquid formulation of claim 15, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, or a tartrate buffer.
20. The stable oral liquid formulation of claim 15, wherein the buffer comprises citric acid and sodium citrate.
21. The stable oral liquid formulation of claim 20, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.
22. The stable oral liquid formulation of claim 15, wherein the buffer comprises citric acid and sodium citrate.
23. The stable oral liquid formulation of claim 15, wherein the buffer comprises phosphoric acid and sodium phosphate.
24. The stable oral liquid formulation of claim 15, wherein the buffer concentration is about 5 mM to about 20 mM.
25. The stable oral liquid formulation of claim 15, wherein the buffer maintains the pH between about 3 and about 3.5.
26. The stable oral liquid formulation of claim 15, wherein the buffer maintains the pH at about 3.3.
27. The stable oral liquid formulation of claim 15, wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 18 months.
28. The stable oral liquid formulation of claim 15, wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 24 months.
29. A stable oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a citrate buffer to maintain the pH about 4.5 or below comprising citric acid and sodium citrate;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

30. The stable oral liquid formulation of claim 29, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.

ENALAPRIL FORMULATIONS

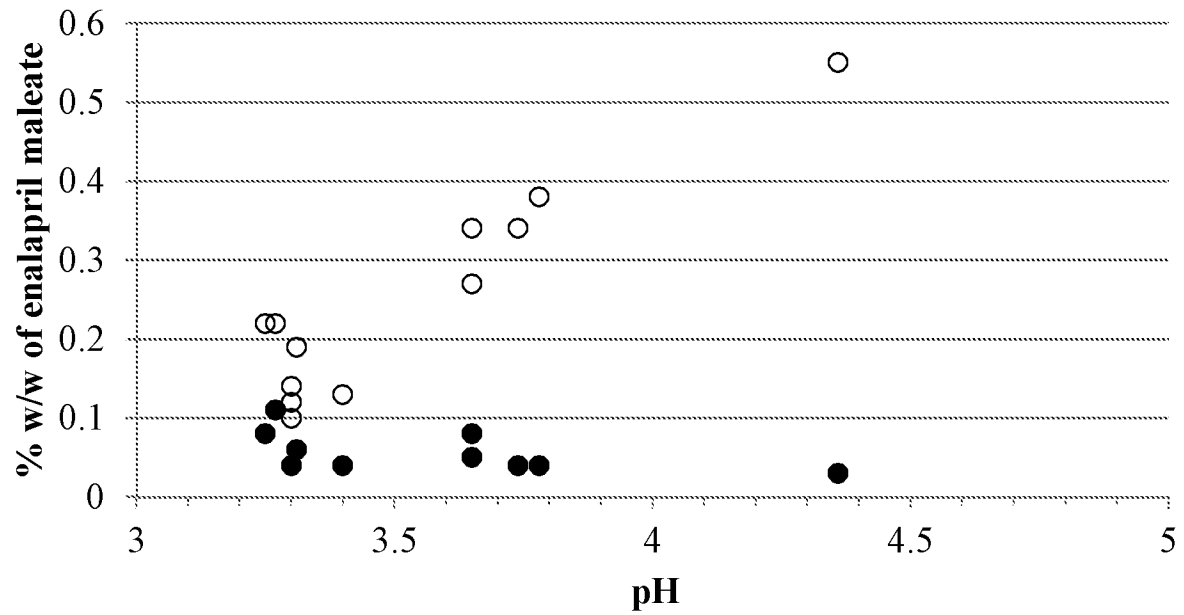
ABSTRACT OF THE DISCLOSURE

Provided herein are stable enalapril oral liquid formulations. Also provided herein are methods of using enalapril oral liquid formulations for the treatment of certain diseases including hypertension, heart failure and asymptomatic left ventricular dysfunction.

1/2

FIG. 1

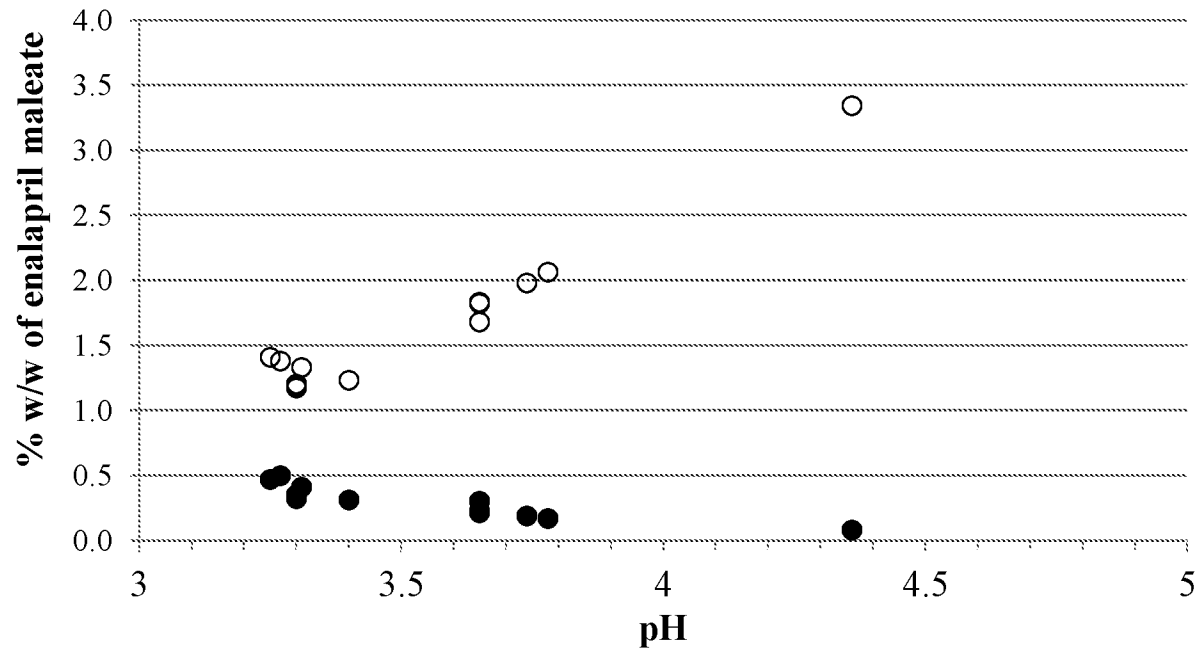
● Enalapril diketopiperazine; ○ Enalaprilat



2/2

FIG. 2

● Enalapril diketopiperazine; ○ Enalaprilat



Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.305
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.</p> <p>This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

Secrecy Order 37 CFR 5.2:

<input type="checkbox"/>	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
--------------------------	---

Inventor Information:

Inventor	1				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Gerold	L.	MOSHER		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	Kansas City	State/Province	MO	Country of Residence	US

Mailing Address of Inventor:

Address 1	12215 Avila Drive				
Address 2					
City	Kansas City	State/Province	MO		
Postal Code	64145	Country	US		

Inventor	2				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	David	W.	MILES		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	Kansas City	State/Province	MO	Country of Residence	US

Mailing Address of Inventor:

Address 1	12309 Wyandotte Street				
Address 2					
City	Kansas City	State/Province	MO		
Postal Code	64145	Country	US		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

SLVGT-EPA_0104365

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.305
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

☐ An Address is being provided for the correspondence information of this application.

Customer Number	21971		
Email Address	patentdocket@wsgr.com	<input type="button" value="Add Email"/>	<input type="button" value="Remove Email"/>

Application Information:

Title of the Invention	ENALAPRIL FORMULATIONS		
Attorney Docket Number	43060-707.305	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	2	Suggested Figure for Publication (if any)	1

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:
☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	<input type="radio"/> US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	21971		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.305
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
	Continuation of	16/177159	2018-10-31		
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/177159	Continuation of	16/003994	2018-06-08	10154987	2018-12-18
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/003994	Continuation of	15802341	2017-11-02	10039745	2018-08-07
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/802341	Continuation of	15/613622	2017-06-05	9808442	2017-11-07
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/613622	Continuation of	15/081603	2016-03-25	9669008	2017-06-06
Prior Application Status	Expired	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
15/081603	Claims benefit of provisional	62/310198	2016-03-18		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.					Add

Foreign Priority Information:

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.305
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.305
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.305
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant	1	Remove
<p>If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.</p> <p style="text-align: right;">Clear</p>		
<input checked="" type="radio"/> Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
<div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
Name of the Deceased or Legally Incapacitated Inventor: <div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>		
Organization Name	Silvergate Pharmaceuticals, Inc.	
Mailing Address Information For Applicant:		
Address 1	6251 Greenwood Plaza Blvd., Bldg. 6, Suite 101	
Address 2		
City	Greenwood Village	State/Province
Country	US	Postal Code
Phone Number		Fax Number
Email Address		
Additional Applicant Data may be generated within this form by selecting the Add button. Add		

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.305
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Assignee	1			
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.				
				<input type="button" value="Remove"/>
If the Assignee or Non-Applicant Assignee is an Organization check here.				<input type="checkbox"/>
Prefix	Given Name	Middle Name	Family Name	Suffix
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Mailing Address Information For Assignee including Non-Applicant Assignee:				
Address 1		<input type="text"/>		
Address 2		<input type="text"/>		
City	<input type="text"/>	State/Province	<input type="text"/>	
Country ⁱ	<input type="text"/>	Postal Code	<input type="text"/>	
Phone Number	<input type="text"/>	Fax Number	<input type="text"/>	
Email Address	<input type="text"/>			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.				<input type="button" value="Add"/>

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Clark Lin/		Date (YYYY-MM-DD)	2019-01-08
First Name	Clark	Last Name	Lin	Registration Number
				67024
Additional Signature may be generated within this form by selecting the Add button.				<input type="button" value="Add"/>

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.305
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

WSGR Docket No. 43060-707.305

PATENT APPLICATION
ENALAPRIL FORMULATIONS

Inventors: Gerold L. Mosher,
Citizen of the United States of America, Residing at
12215 Avila Drive
Kansas City, MO 64145

David W. Miles,
Citizen of the United States of America, Residing at
12309 Wyandotte Street
Kansas City, MO 64145

Assignees: Silvergate Pharmaceuticals, Inc.
6251 Greenwood Plaza Blvd., Bldg. 6, Suite 101
Greenwood Village, CO 80111

a Delaware Corporation

Entity: Large business concern



Wilson Sonsini Goodrich & Rosati
PROFESSIONAL CORPORATION

650 Page Mill Road
Palo Alto, CA 94304
(650) 493-9300 (Main)
(650) 493-6811 (Facsimile)

Filed Electronically on: January 8, 2019

ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

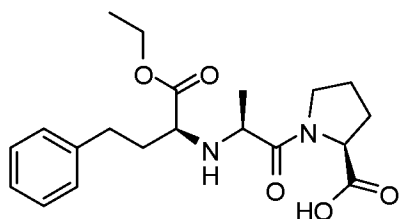
[0001] This application is a continuation of U.S. Patent Application No. 16/177,159, filed October 31, 2018, which is a continuation of U.S. Patent Application No. 16/003,994, filed June 8, 2018, which is a continuation of U.S. Patent Application No. 15/802,341, filed November 2, 2017 (now U.S. Patent No. 10,039,745, issued August 7, 2018), which is a continuation of U.S. Patent Application No. 15/613,622, filed June 5, 2017 (now U.S. Patent No. 9,808,442, issued November 7, 2017), which is a continuation of U.S. Patent Application No. 15/081,603, filed March 25, 2016 (now U.S. Patent No. 9,669,008, issued June 06, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed March 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

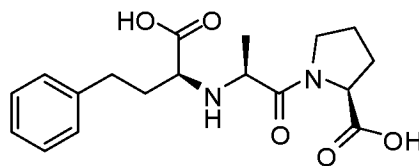
[0002] Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

[0003] A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

[0004] Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



Enalapril



Enalaprilat

[0005] Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

[0006] Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0007] In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25 % (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18 % (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47 % (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11 % (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25 % (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 18 months. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 24

months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0008] In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0009] In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 18 months. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0010] In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3 % (w/w of solids) enalapril maleate; (ii) about 13.5 % (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2 % (w/w of solids) citric acid; (iv) about 19.3 % (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0011] In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9 % (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 18 months. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0012] In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the

formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0013] Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0014] In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

[0015] Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0016] In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

[0017] Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments,

the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0018] Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

[0019] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0021] FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5°C.

[0022] FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22°C).

DETAILED DESCRIPTION OF THE INVENTION

[0023] Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

[0024] It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

[0025] Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

[0026] For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

[0027] Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

[0028] The present embodiments described herein provide a safe and effective oral administration of enalapril for the treatment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

[0029] As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in

the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

[0030] Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

[0031] Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

[0032] In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

[0033] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84

mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

[0034] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 % w/w to about 30 % w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 % w/w, about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 % w/w, about 14 % w/w, about 14.5 % w/w, about 15 % w/w, about 15.1 % w/w, about 15.2 % w/w, about 15.3 % w/w, about 15.4 % w/w, about 15.5 % w/w, about 15.6 % w/w, about 15.7 % w/w, about 15.8 % w/w, about 15.9 % w/w, about 16 % w/w, about 16.1 % w/w, about 16.2 % w/w, about 16.3 % w/w, about 16.4 % w/w, about 16.5 % w/w, about 16.6 % w/w, about 16.7 % w/w, about 16.8 % w/w, about 16.9 % w/w, about 17 % w/w, about 17.1 % w/w, about 17.2 % w/w, about 17.3 % w/w, about 17.4 % w/w, about 17.5 % w/w, about 17.6 % w/w, about 17.7 % w/w, about 17.8 % w/w, about 17.9 % w/w, about 18 % w/w, about 18.1 % w/w, about 18.2 % w/w, about 18.3 % w/w, about 18.4 % w/w, about 18.5 % w/w, about 18.6 % w/w, about 18.7 % w/w, about 18.8 % w/w, about 18.9 % w/w, about 19 % w/w, about 19.1 % w/w, about 19.2 % w/w, about 19.3 % w/w, about 19.4 % w/w, about 19.5 % w/w, about 19.6 % w/w, about 19.7 % w/w, about 19.8 % w/w, about 19.9 % w/w, about 20 % w/w, about 20.1 % w/w, about 20.2 % w/w, about 20.3 % w/w, about 20.4 % w/w, about 20.5 % w/w, about 20.6 % w/w, about 20.7 % w/w, about 20.8 % w/w, about 20.9 % w/w, about 21 % w/w, about 21.1 % w/w, about 21.2 % w/w, about 21.3 % w/w, about 21.4 % w/w, about 21.5 % w/w, about 21.6 % w/w, about 21.7 % w/w, about 21.8 % w/w, about 21.9 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5

% w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10 % w/w to about 25 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5 % w/w of the solids in the oral liquid formulation.

[0035] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1 % w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1 % w/w, about 0.15 % w/w, about 0.2 % w/w, about 0.25 % w/w, about 0.3 % w/w, about 0.35 % w/w, about 0.4 % w/w, about 0.45 % w/w, about 0.5 % w/w, about 0.55 % w/w, about 0.6 % w/w, about 0.65 % w/w, about 0.7 % w/w, about 0.75 % w/w, about 0.8 % w/w, about 0.85 % w/w, about 0.9 % w/w, about 0.95 % w/w, or about 1 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4 % w/w to about 0.7 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6 % w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

[0036] Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

[0037] Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate,

saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet AmTM liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet AmTM powder (Product Code 918.005--maltodextrin, sorbitol, and fructose combination and Product Code 918.010--water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweetTM (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), MaltisweetTM (maltitol solution, Ingredion), SorboTM (sorbitol and sorbitol/xylitol solution, SPI Polyols), InvertoseTM (high fructose corn syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

[0038] In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

[0039] In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

[0040] In some embodiments, sucralose is present in about 1 % w/w to about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about

13.5 % w/w, about 14% w/w, about 14.5 % w/w, about 15 % w/w, about 15.5 % w/w, about 16 % w/w, about 16.5 % w/w, about 17 % w/w, about 17.5 % w/w, about 18 % w/w, about 18.5 % w/w, about 19 % w/w, about 19.5 % w/w, about 20 % w/w, about 20.5 % w/w, about 21 % w/w, about 21.5 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5 % w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8 % w/w to about 18 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5 % w/w of the solids in the oral liquid formulation.

[0041] In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

[0042] In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

[0043] In some embodiments, xylitol is present in about 80 % w/w to about 99 % w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80 % w/w, about 81 % w/w, about 82 % w/w, about 83 % w/w, about 84 % w/w, about 85 % w/w, about 86 % w/w, about 87 % w/w, about 88 % w/w, about 89 % w/w, about 90 % w/w, about 91 % w/w, about 92 % w/w, about 93 % w/w, about 94 % w/w, about 95 % w/w, about 96 % w/w, about 97 % w/w, about 98 % w/w, or about 99 % w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96 % w/w to about 98 % w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96 % w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

[0044] Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

[0045] In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

[0046] In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

[0047] In some embodiments, the preservative is sodium benzoate.

[0048] In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

[0049] In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

[0050] In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about

1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

[0051] In some embodiments, sodium benzoate is present in about 1% w/w to about 30 % w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 % w/w, about 14 % w/w, about 14.5 % w/w, about 15 % w/w, about 15.1 % w/w, about 15.2 % w/w, about 15.3 % w/w, about 15.4 % w/w, about 15.5 % w/w, about 15.6 % w/w, about 15.7 % w/w, about 15.8 % w/w, about 15.9 % w/w, about 16 % w/w, about 16.1 % w/w, about 16.2 % w/w, about 16.3 % w/w, about 16.4 % w/w, about 16.5 % w/w, about 16.6 % w/w, about 16.7 % w/w, about 16.8 % w/w, about 16.9 % w/w, about 17 % w/w, about 17.1 % w/w, about 17.2 % w/w, about 17.3 % w/w, about 17.4 % w/w, about 17.5 % w/w, about 17.6 % w/w, about 17.7 % w/w, about 17.8 % w/w, about 17.9 % w/w, about 18 % w/w, about 18.1 % w/w, about 18.2 % w/w, about 18.3 % w/w, about 18.4 % w/w, about 18.5 % w/w, about 18.6 % w/w, about 18.7 % w/w, about 18.8 % w/w, about 18.9 % w/w, about 19 % w/w, about 19.1 % w/w, about 19.2 % w/w, about 19.3 % w/w, about 19.4 % w/w, about 19.5 % w/w, about 19.6 % w/w, about 19.7 % w/w, about 19.8 % w/w, about 19.9 % w/w, about 20 % w/w, about 20.1 % w/w, about 20.2 % w/w, about 20.3 % w/w, about 20.4 % w/w, about 20.5 % w/w, about 20.6 % w/w, about 20.7 % w/w, about 20.8 % w/w, about 20.9 % w/w, about 21 % w/w, about 21.1 % w/w, about 21.2 % w/w, about 21.3 % w/w, about 21.4 % w/w, about 21.5 % w/w, about 21.6 % w/w, about 21.7 % w/w, about 21.8 % w/w, about 21.9 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5 % w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5 % w/w of the solids in the oral liquid formulation.

[0052] In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1 % w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1 % w/w, about 0.15 % w/w, about 0.2 % w/w, about 0.25 % w/w, about 0.3 % w/w, about 0.35 % w/w, about 0.4 % w/w, about 0.45 % w/w, about 0.5 % w/w, about 0.55 % w/w, about 0.6 % w/w, about 0.65 % w/w, about 0.7 % w/w, about 0.75 % w/w, about 0.8 % w/w, about 0.85 % w/w, about 0.9 % w/w, about 0.95 % w/w, or about 1 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4 % w/w to about 0.7 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6 % w/w of the solids in the oral liquid formulation.

[0053] In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

[0054] In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

[0055] In some embodiments, the paraben or mixture of parabens is present in about 2 % w/w to about 30 % w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2 % w/w, about 3 % w/w, about 4 % w/w, about 5 % w/w, about 6 % w/w, about 7 % w/w, about 8 % w/w, about 9 % w/w, about 10 % w/w, about 11 % w/w, about 12 % w/w, about 13 % w/w, about 14 % w/w, about 15 % w/w, about 16 % w/w, about 17 % w/w, about 18 % w/w, about 19 % w/w, about 20 % w/w, about 21 % w/w, about 22 % w/w, about 23 % w/w, about 24 % w/w, about 25 % w/w, about 26 % w/w, about 27 % w/w, about 28 % w/w, about 29 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2 % w/w to about 3 % w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23 % w/w to about 26 % w/w of the

solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26 % w/w to about 30 % w/w of the solids in the oral liquid formulation.

Sweetener and preservative incompatibility

[0056] Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

[0057] In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

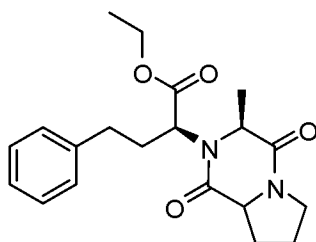
[0058] Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

[0059] In some embodiments, the oral liquid formulation comprises a buffer.

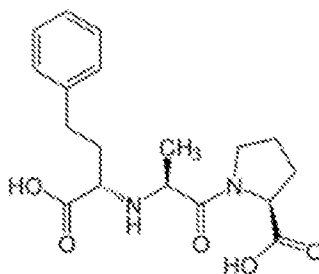
[0060] In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

[0061] In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

[0062] In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



enalapril diketopiperazine;



enalaprilat

[0063] In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

[0064] In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

[0065] In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

[0066] In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM,

about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

[0067] In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

[0068] In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1

mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

[0069] In some embodiments, citric acid is present in about 10 % w/w to about 50 % w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10 % w/w, about 11 % w/w, about 12 % w/w, about 13 % w/w, about 14 % w/w, about 15 % w/w, about 16 % w/w, about 17 % w/w, about 18 % w/w, about 19 % w/w, about 20 % w/w, about 21 % w/w, about 22 % w/w, about 23 % w/w, about 24 % w/w, about 25 % w/w, about 26 % w/w, about 27 % w/w, about 28 % w/w, about 29 % w/w, about 30 % w/w, about 31 % w/w, about 32 % w/w, about 33 % w/w, about 34 % w/w, about 35 % w/w, about 36 % w/w, about 37 % w/w, about 38 % w/w, about 39 % w/w, about 40 % w/w, about 41 % w/w, about 42 % w/w, about 43 % w/w, about 44 % w/w, about 45 % w/w, about 46 % w/w, about 47 % w/w, about 48 % w/w, about 49 % w/w, about 50 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19 % w/w of the solids in the oral liquid formulation.

[0070] In some embodiments, citric acid is present in about 1 % w/w to about 5 % w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1 % w/w, about 1.1 % w/w, about 1.2 % w/w, about 1.3 % w/w, about 1.4 % w/w, about 1.5 % w/w, about 1.6 % w/w, about 1.7 % w/w, about 1.8 % w/w, about 1.9 % w/w, about 2 % w/w, about 2.1 % w/w, about 2.2 % w/w, about 2.3 % w/w, about 2.4 % w/w, about 2.5 % w/w, about 2.6 % w/w, about 2.7 % w/w, about 2.8 % w/w, about 2.9 % w/w, about 3 % w/w, about 3.1 % w/w, about 3.2 % w/w, about 3.3 % w/w, about 3.4 % w/w, about 3.5 % w/w, about 3.6 % w/w, about 3.7 % w/w, about 3.8 % w/w, about 3.9 % w/w, about 4 % w/w, about 4.1 % w/w, about 4.2 % w/w, about 4.3 % w/w, about 4.4 % w/w, about 4.5 % w/w, about 4.6 % w/w, about 4.7 % w/w, about 4.8 % w/w, about 4.9 % w/w, or about 5 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6 % w/w of the solids in the oral liquid formulation.

[0071] In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid

formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/ml, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

[0072] In some embodiments, sodium citrate dihydrate is present in about 1 % w/w to about 15 % w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1 % w/w, about 1.1 % w/w, about 1.2 % w/w, about 1.3 % w/w, about 1.4 % w/w, about 1.5 % w/w, about 1.6 % w/w, about 1.7 % w/w, about 1.8 % w/w, about 1.9 % w/w, about 2 % w/w, about 2.1 % w/w, about 2.2 % w/w, about 2.3 % w/w, about 2.4 % w/w, about 2.5 % w/w, about 2.6 % w/w, about 2.7 % w/w, about 2.8 % w/w, about 2.9 % w/w, about 3 % w/w, about 3.1 % w/w, about 3.2 % w/w, about 3.3 % w/w, about 3.4 % w/w, about 3.5 % w/w, about 3.6 % w/w, about 3.7 % w/w, about 3.8 % w/w, about 3.9 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 % w/w, about 14 % w/w, about 14.5 % w/w, about 15 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5 % w/w of the solids

in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9 % w/w of the solids in the oral liquid formulation.

[0073] In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional excipients

[0074] In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

[0075] Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

[0076] In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

[0077] In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

[0078] Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches,

pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

[0079] Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, PA: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, PA: Mack Publishing Co 1975); Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, NY: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

[0080] The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

[0081] The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95 % or greater of the initial enalapril amount and about 5 % w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5 % w/w, about 4 % w/w, about 3 % w/w, about 2.5 % w/w, about 2 % w/w, about 1.5 % w/w, about 1 % w/w, or about 0.5 % w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1 % w/w total impurities or related substances.

[0082] At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5 ± 3 °C. In some embodiments, refrigerated condition is about 2 °C, about 2.1 °C, about 2.2 °C, about 2.3 °C, about 2.4 °C, about 2.5 °C, about 2.6 °C, about 2.7 °C, about 2.8 °C, about 2.9 °C, about 3 °C, about 3.1 °C, about 3.2 °C, about 3.3 °C, about 3.4 °C, about 3.5 °C, about 3.6 °C, about 3.7 °C, about 3.8 °C, about 3.9 °C, about 4 °C, about 4.1 °C, about 4.2 °C,

about 4.3 °C, about 4.4 °C, about 4.5 °C, about 4.6 °C, about 4.7 °C, about 4.8 °C, about 4.9 °C, about 5 °C, about 5.1 °C, about 5.2 °C, about 5.3 °C, about 5.4 °C, about 5.5 °C, about 5.6 °C, about 5.7 °C, about 5.8 °C, about 5.9 °C, about 6 °C, about 6.1 °C, about 6.2 °C, about 6.3 °C, about 6.4 °C, about 6.5 °C, about 6.6 °C, about 6.7 °C, about 6.8 °C, about 6.9 °C, about 7 °C, about 7.1 °C, about 7.2 °C, about 7.3 °C, about 7.4 °C, about 7.5 °C, about 7.6 °C, about 7.7 °C, about 7.8 °C, about 7.9 °C, or about 8 °C. At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. 25±5 °C; 55±10% RH). In some instances, an accelerated condition is at about 25 °C, about 30 °C, about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C or about 60 °C. In other instances, an accelerated condition is above 55% RH, about 65 % RH, about 70 % RH, about 75 % RH or about 80 % RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40 °C at 75±5 % RH humidity.

Enalapril Oral Powder Formulation

[0083] In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

[0084] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30 % w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 % w/w, about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 %

w/w, about 14% w/w, about 14.5 % w/w, about 15 % w/w, about 15.5 % w/w, about 16 % w/w, about 16.5 % w/w, about 17 % w/w, about 17.5 % w/w, about 18 % w/w, about 18.5 % w/w, about 19 % w/w, about 19.5 % w/w, about 20 % w/w, about 20.5 % w/w, about 21 % w/w, about 21.5 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5 % w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5 % w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5 % w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5 % w/w of the powder formulation. In some embodiments, enalapril is present in about 18 % w/w of the powder formulation.

[0085] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1 % w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1 % w/w, about 0.15 % w/w, about 0.2 % w/w, about 0.25 % w/w, about 0.3 % w/w, about 0.35 % w/w, about 0.4 % w/w, about 0.45 % w/w, about 0.5 % w/w, about 0.55 % w/w, about 0.6 % w/w, about 0.65 % w/w, about 0.7 % w/w, about 0.75 % w/w, about 0.8 % w/w, about 0.85 % w/w, about 0.9 % w/w, about 0.95 % w/w, or about 1 % w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4 % w/w to about 0.7 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6 % w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4 % w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5 % w/w of the powder formulation.

[0086] Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1 % w/w to about 30 % w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1 % w/w to about 30 % w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1 % w/w to about 30 % w/w of the solids in the oral liquid formulation, in an analogous enalapril

powder formulation sodium benzoate is present in about 1 % w/w to about 30 % w/w in the powder formulation.

[0087] Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

[0088] Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

[0089] In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

[0090] Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon

dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

[0091] In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

[0092] In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

[0093] In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

[0094] Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, PA: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, PA: Mack Publishing Co 1975); Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, NY: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

[0095] In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

[0096] Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof; and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2x10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

[0097] The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder

formulations having about 95 % or greater of the initial enalapril amount and 5 % w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5 % w/w, about 4 % w/w, about 3 % w/w, about 2.5 % w/w, about 2 % w/w, about 1.5 % w/w, about 1 % w/w, or about 0.5 % w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1 % w/w total impurities or related substances.

[0098] At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25 ± 4 °C; 55 ± 10 % RH). In some instances, an accelerated condition is at about 30 °C, about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C or about 60 °C. In other instances, an accelerated condition is above 65 % RH, about 70 % RH, about 75 % RH or about 80 % RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40 °C at 75 ± 5 % RH humidity.

Kits and Articles of Manufacture

[0099] For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

[00100] A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

[00101] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

[00102] Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

[00103] In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

[00104] In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described

herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

[00105] In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

[00106] In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

[00107] Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

[00108] In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but

can nevertheless be determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

[00109] In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76, mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

[00110] In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg,

about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

[00111] In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

[00112] In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

[00113] Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[00114] In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular

disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

[00115] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

[00116] In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00117] In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, *i.e.*, administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (*e.g.* drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

[00118] In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

[00119] In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10

minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

[00120] In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

[00121] The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

[00122] Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxybenzamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltiazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, losartan, eprosartin, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

[00123] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[00124] As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

[00125] The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[00126] “Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

[00127] As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

[00128] “Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

[00129] The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms “patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic

species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

[00130] By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[00131] The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[00132] A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

[00133] The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the

condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, “treat,” “treated,” “treatment,” or “treating” includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60 °C.

[00134] Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60 °C heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

[00135] The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at 60 °C	Formulation					
	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60 °C.

[00136] Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60 °C heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5mM citrate)	B2 (10mM citrate)	B3 (20mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7

Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

[00137] The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours at 60°C	Formulation		
	B1 (5mM citrate)	B2 (10mM citrate)	B3 (20mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives.

[00138] Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula[®] mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5 °C ± 3°C, at room temperature (19-23 °C) and at 40°C ± 2 °C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Powder Formulation (grams)					
Component	C1	C2	C3	C4	C5
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

[00139] The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	°C	Weeks	C1	C2	C3	C4	C5
Liquid Formulations							
Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
		4	0.02	0.03	0.03	0.03	0.02
		8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.04	0.02	0.02
		4	0.05	0.09	0.11	0.05	0.04
		8	0.08	0.17	0.19		
	40	0	0.03	0.04	0.04	0.02	0.02
		4	0.35	0.91	1.10	0.31	0.21
		8	0.65	1.80	2.05		
Enalaprilat	5	0	0.18	0.14	0.12	0.13	0.19
		4	0.18	0.15	0.12	0.43	0.53
		8	0.55	0.38	0.34		
	19-23	0	0.18	0.14	0.12	0.13	0.19
		4	1.35	0.83	0.80	1.75	2.29
		8	3.34	2.06	1.98		
	40	0	0.18	0.14	0.12	0.13	0.19
		4	10.49	6.08	6.11	12.30	16.14
		8	24.37	14.12	14.22		

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative.

[00140] Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The

amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, at room temperature ($19\text{-}23^{\circ}\text{C}$) and at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations						
Powder Formulation (grams)						
Component	D1	D2	D3	D4	D5	D6
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

[00141] The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)								
Storage			Formulation					
	°C	Weeks	D1	D2	D3	D4	D5	D6
Liquid Formulations								
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		
	40	0	0.03	0.02	0.03	0.03	0.13	0.14

4	4.76	4.42	4.76	6.45	5.55	5.24
8	8.95	8.64	9.61	12.94	12.73	12.18
12	11.01	10.64	11.41	16.16		
26	17.18	17.11	18.30	27.36		

Example E: Stability of Solution Formulations of Enalapril Maleate.

[00142] Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5 °C ± 3 °C, at room temperature (19-23 °C) and at 40 °C ± 2 °C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

[00143] The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	°C	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04

		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
	19-23	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28
		12	0.58	0.59	0.53	0.51	0.48	0.45
		26	1.10	1.10	1.00	0.95	0.97	0.92
		52					2.30	2.15
		62	3.02	3.04	2.75	2.64		
	40	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76	1.68
		8	4.02	3.99	3.99	3.62	3.37	3.13
		12	6.72	6.42	6.47	6.00	5.53	5.29
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		
	19-23	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.65	0.65	0.68	0.70	0.50	0.46
		8	1.17	1.19	1.20	1.23	1.03	0.95
		12	1.67	1.69	1.72	1.80	1.30	1.21
		26	3.36	3.38	3.42	3.57	3.07	2.90
		52					6.32	5.88
		62	7.99	8.02	8.04	8.57		
	40	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	4.85	4.93	5.19	5.42	3.33	3.25
		8	8.08	8.06	8.56	9.01	6.65	6.35
		12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5 °C and 19-23 °C.

[00144] The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in Figure 1 (5°C ± 3 °C) and Figure 2 (19-23 °C storage). These formulations all contained 20mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

[00145] Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10mg Enalapril Maleate Oral Solution vs. 10mg Epaned[®] Powder for Oral Solution (Reconstituted) Under Fasted Conditions

[00146] The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned[®] (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

[00147] Study design: Thirty-two healthy adult subjects received a single 10mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

[00148] During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

[00149] Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix[™] WinNonlin[®] (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

[00150] Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned

Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_{\max} were approximately 115% and 109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{\max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{\text{last}})$ and $\ln(AUC_{\text{inf}})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

[00151] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: <i>Not Yet Assigned</i>
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 1032
Serial No.: 16/242,898	Examiner: <i>Not Yet Assigned</i>
Filed: January 8, 2019	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<hr/> <p style="text-align: center;"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Preliminary Amendment and all marked attachments are being deposited by Electronic Filing on January 18, 2019, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: _____ /Rose Andico/ Rose Andico</p>

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Commissioner:

Applicant respectfully requests entry of the proposed amendments prior to examination and allowance of the pending claims.

Amendments to the Claims begin on page 2.

Remarks begin on page 6.

Conclusion begins on page 7.

U.S. Patent Application No. 43060-707.305
Preliminary Amendment

Attorney Docket No.: 43060-707.305

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Amendments to the claims were made for purposes of more clearly stating the claimed subject matter and do not add new matter or alter the scope of the claims.

Listing of the Claims:

1. (Original) A stable oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
2. (Original) The stable oral liquid formulation of claim 1 further comprising a sweetener.
3. (Original) The stable oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. (Original) The stable oral liquid formulation of claim 1 further comprising a flavoring agent.
5. (Currently Amended) The stable oral liquid formulation of claim 1, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, or a tartrate buffer.
6. (Original) The stable oral liquid formulation of claim 1, wherein the buffer comprises citric acid and sodium citrate.

U.S. Patent Application No. 43060-707.305
Preliminary Amendment

Attorney Docket No.: 43060-707.305

7. (Original) The stable oral liquid formulation of claim 6, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.
8. (Original) The stable oral liquid formulation of claim 1, wherein the buffer comprises phosphoric acid and sodium phosphate.
9. (Original) The stable oral liquid formulation of claim 1, wherein the buffer concentration is about 5 mM to about 20 mM.
10. (Original) The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH between about 3 and about 4.
11. (Original) The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH at about 3.3.
12. (Original) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 18 months.
13. (Original) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 24 months.
14. (Currently Amended) A stable oral liquid formulation, consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer to maintain the pH about 4.5 or below;

(iii) about 1 mg/ml of a preservative that is sodium benzoate; and

(iv) water;

wherein the formulation optionally comprises a sweetener and/or a flavoring agent and is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

U.S. Patent Application No. 43060-707.305
Preliminary Amendment

Attorney Docket No.: 43060-707.305

15. (Currently Amended) A stable oral liquid formulation, comprising:

- (i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer to maintain the pH about 4.5 or below;
- (iii) about ~~19.3~~ 19% (w/w of solids) of a preservative that is sodium benzoate; and
- (iv) water;

wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

16. (Original) The stable oral liquid formulation of claim 15 further comprising a sweetener.

17. (Original) The stable oral liquid formulation of claim 16, wherein the sweetener is sucralose.

18. (Original) The stable oral liquid formulation of claim 15 further comprising a flavoring agent.

19. (Original) The stable oral liquid formulation of claim 15, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, or a tartrate buffer.

20. (Original) The stable oral liquid formulation of claim 15, wherein the buffer comprises citric acid and sodium citrate.

21. (Original) The stable oral liquid formulation of claim 20, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.

22. (Original) The stable oral liquid formulation of claim 15, wherein the buffer comprises citric acid and sodium citrate.

23. (Original) The stable oral liquid formulation of claim 15, wherein the buffer comprises phosphoric acid and sodium phosphate.

U.S. Patent Application No. 43060-707.305
Preliminary Amendment

Attorney Docket No.: 43060-707.305

24. (Original) The stable oral liquid formulation of claim 15, wherein the buffer concentration is about 5 mM to about 20 mM.
25. (Original) The stable oral liquid formulation of claim 15, wherein the buffer maintains the pH between about 3 and about 3.5.
26. (Original) The stable oral liquid formulation of claim 15, wherein the buffer maintains the pH at about 3.3.
27. (Original) The stable oral liquid formulation of claim 15, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 18 months.
28. (Original) The stable oral liquid formulation of claim 15, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 24 months.
29. (Original) A stable oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a citrate buffer to maintain the pH about 4.5 or below comprising citric acid and sodium citrate;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
30. (Original) The stable oral liquid formulation of claim 29, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.

U.S. Patent Application No. 43060-707.305
Preliminary Amendment

Attorney Docket No.: 43060-707.305

REMARKS

Claims 1-30 are currently pending in this application. Applicant respectfully requests entry of this Preliminary Amendment where claims 5, 14, and 15 have been amended. No new matter has been added.

U.S. Patent Application No. 43060-707.305
Preliminary Amendment

Attorney Docket No.: 43060-707.305

CONCLUSION

This Preliminary Amendment is being filed prior to examination on the merits. Applicant respectfully requests entry of the claims as amended and solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (617) 598-7823.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: January 18, 2019

By: /Clark Lin/

Clark Y. Lin, Ph.D., Esq.
Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (617) 598-7823
Customer No. 021971



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/242,898	01/08/2019		3180	43060-707.305	30	4

CONFIRMATION NO. 1032

FILING RECEIPT

21971

WILSON, SONSINI, GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050



CC000000103521838

Date Mailed: 02/04/2019

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Gerold L. MOSHER, Kansas City, MO;
 David W. MILES, Kansas City, MO;

Applicant(s)

Silvergate Pharmaceuticals, Inc., Greenwood Village, CO;

Power of Attorney: The patent practitioners associated with Customer Number 21971

Domestic Priority data as claimed by applicant

This application is a CON of 16/177,159 10/31/2018
 which is a CON of 16/003,994 06/08/2018 PAT 10154987
 which is a CON of 15/802,341 11/02/2017 PAT 10039745
 which is a CON of 15/613,622 06/05/2017 PAT 9808442
 which is a CON of 15/081,603 03/25/2016 PAT 9669008
 which claims benefit of 62/310,198 03/18/2016

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 01/31/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/242,898**

Projected Publication Date: 05/16/2019

Non-Publication Request: No

Early Publication Request: No

Title

ENALAPRIL FORMULATIONS

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/242,898	01/08/2019	Gerold L. MOSHER	43060-707.305	1032
21971 7590 02/14/2019 WILSON, SONSINI, GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 94304-1050			EXAMINER	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			02/14/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

<i>Decision Granting Request for Prioritized Examination (Track I)</i>	Application No. 16/242,898	Applicant(s) MOSHER et al.	
	Examiner BRIAN W BROWN	Art Unit OPET	AIA (First Inventor to File) Status Yes

1. THE REQUEST FILED 08 January 2019 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).

B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to BRIAN BROWN at (571)272-5338. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/BRIAN W BROWN/ Petitions Examiner, OPET	
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/242,898	01/08/2019	Gerold L. MOSHER	43060-707.305	1032
21971	7590	05/02/2019		
WILSON, SONSINI, GOODRICH & ROSATI				
650 PAGE MILL ROAD				
PALO ALTO, CA 94304-1050				
			EXAMINER	
			SPRINGER, STEPHANIE K	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			05/02/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary**Application No.**

16/242,898

Applicant(s)

MOSHER et al.

Examiner

STEPHANIE K SPRINGER

Art Unit

1629

AIA (FITF) Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 18 January 2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a) ☐ This action is **FINAL**.

2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) 8 and 23 is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1-7,9-22 and 24-30 is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date ____.

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: ____.

Paper No(s)/Mail Date 14 pgs, 2/5/19.

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Art Unit: 1629

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DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Status

This application is a continuation of application 16/177,159, filed on October 31, 2018, which is a continuation of application 16/003,994, now US Patent 10,154,987, filed on June 8, 2018, which is a continuation of application 15/802,341, now US Patent 10,039,745, filed on November 2, 2017, which is a continuation of application 15/613,622, now US Patent 9,808,442, filed on June 5, 2017, which is a continuation of application 15/081,603, now US Patent 9,669,008, filed on March 25, 2016 and claims priority to US provisional application 62/310,198, filed on March 18, 2016.

This application was granted Track One status on February 14, 2019.

Claims 1-30 are pending and are the subject of the Office Action below.

Election of Species

Claims 1-30 are generic to the following disclosed patentably distinct species: buffers to maintain the pH about 4.5 or below, *i.e.*, the species recited at, *inter alia*, claims 6 and 7, and in the specification at paragraph 88.

The species are independent or distinct because the genus of buffers to maintain the pH about 4.5 or below encompasses a vast number of different species, requiring different search queries, the prior art applicable to one species would not likely be applicable to another species, and the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. In addition, these species are not obvious variants of each other based on the current record.

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Applicant is required under 35 U.S.C. 121 to elect a single disclosed species of buffer to maintain the pH about 4.5 or below for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. In other words, the Applicant is required to elect a species of buffer to maintain the pH about 4.5 or below, *i.e.*, one of the species recited in paragraph 88 of the specification.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reasons apply: the prior art applicable to one invention would not likely be applicable to another invention, and the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or a grouping of patentably indistinct species to be examined even though the requirement may be traversed (37 CFR § 1.143) and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. **If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse.** Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR § 1.144. If claims are added after the election, Applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should Applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, Applicant should

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submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR § 1.141.

Telephonic Election

During a telephone conversation with Clark Lin, Reg. No. 67,024, on February 27, 2019, a provisional election was made without traverse to prosecute the buffer species wherein the buffer comprises citric acid and sodium citrate, as recited in instant claims 6, 7, 20-22, 29, and 30. Affirmation of this election must be made by applicant in replying to this Office action. Claims 8 and 23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-7, 9-22, and 24-30 are examined on the merits herein as they read upon the elected species.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on February 5, 2019 has been considered by the examiner. The submissions are in compliance with the provisions of 37 CFR §§ 1.97 and 1.98. Enclosed with this Office Action is a return-copy of the Forms PTO-1449 with the examiner's initials and signature indicating those references that have been considered.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-7, 9-22, and 24-30 are rejected under 35 U.S.C. 103 as obvious over Nahata et al., "Stability of elanapril maleate in three extemporaneously prepared oral liquids", *Am. J. Health-Syst. Pharm.*, 1998, vol. 55, pages 1155-1157 (cited in IDS) in view of Sosnowska et al., "Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared From Commercially Available Tablets", *Acta Poloniae Pharmaceutica – Drug Research*, 2009, vol. 66, no. 3, pages 321-326 (cited in PTO-892) in view of Boukarim et al., "Preservatives in Liquid Pharmaceutical Preparations", *J. Appl. Res.*, 2009, vol. 9, no. 1&2, pages 14-17 (cited in PTO-892).

Claims 1-7, 9-22, and 24-30 are generally drawn to compositions comprising:

- (i) about 0.6 to about 1.2 mg/ml, or about 10% to about 25% (w/w/ of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer to maintain the pH about 4.5 or below;
- (iii) about 1 mg/ml or 19% (w/w of solids) of a preservative that is sodium benzoate; and
- (iv) water.

Nahata teaches formulations comprising

- (i) 1 mg/ml enalapril;
- (ii) a buffer comprising citric acid and sodium citrate;

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(iii) a preservative; and

(iv) water.

In particular, Nahata teaches preparation of an aqueous solution comprising 1 mg/ml enalapril in a citrate buffer solution (page 1156, column 1, paragraph 2). The citrate buffer solution is prepared accordingly: "Prepare the isotonic citrate buffer solution (pH 5.0) by dissolving 0.353 g of Citric Acid Monohydrate Granular, USP, 1.01 g of Sodium Citrate Dihydrate Granular, USP, and 0.54 g of sodium chloride in 100 mL of distilled water" (page 1157, Appendix and footnote a). The ordinarily skilled artisan would recognize the sodium chloride in the citrate buffer solution taught by Nahata to meet the instant requirements of a preservative; see Parish, "How do salt and sugar prevent microbial spoilage?", *Scientific American*, 2006 (cited in PTO-892; cited to show a fact).

Nahata also teaches an aqueous solution comprising 1 mg/ml enalapril in a mixture of Ora-Sweet and Ora-Plus (page 1156, column 1, paragraph 2). Ora-Sweet and Ora-Plus are commercially available from Paddock Laboratories (page 1157, footnotes d and e). Ora-Sweet is an aqueous solution comprising sucrose, glycerin, sorbitol, flavoring, citric acid, sodium phosphate, methylparaben, and potassium sorbate; Ora-Plus is an aqueous solution comprising microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, flavoring, citric acid, sodium phosphate, simethicone, methylparaben, and potassium sorbate; both Ora-Sweet and Ora-Plus have a pH of 4.2. Thus, the formulation taught by Nahata comprising 1 mg/ml enalapril in a mixture of Ora-Sweet and Ora-Plus comprises

(i) 1 mg/ml enalapril;

(ii) citric acid;

(iii) a preservative, such as methylparaben; and

(iv) water.

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The formulations comprising Ora-Sweet and Ora-Plus also comprise sweeteners and flavoring agents, while not containing mannitol or silicon dioxide, thereby meeting the requirements of claims 2, 4-7, 16-22, 29, and 30.

Thus, Nahata teaches aqueous compositions comprising

- (i) 1 mg/ml enalapril;
- (ii) citric acid and sodium citrate;
- (iii) a preservative, such as methylparaben; and
- (iv) water.

Similarly, Sosnowska teaches formulations comprising

- (i) 1 mg/ml enalapril;
- (ii) citric acid and citrate buffer;
- (iii) 0.2% methylhydroxybenzoate as a preservative, *i.e.*, methylparaben; and
- (iv) water.

Sosnowska teaches liquid formulations of enalapril, prepared from crushed enalapril tablets. Sosnowska generally teaches compositions comprising enalapril maleate in deionized water, citrate buffer solution, carboxymethylcellulose as a suspending agent, and methyl hydroxybenzoate 0.2% as a preservative. Sosnowska teaches that the maximum stability of enalapril maleate is at a pH of about 3; “therefore the pH value of prepared formulations was adjusted to 3.0 using citric acid” (page 322, column 1, “Formulations preparation”). Regarding stability, Sosnowska notes:

“The tablet suspension in water would be expected to readily support microbial growth, especially at room temperature during in-use conditions, therefore 0.2% methyl hydroxybenzoate as compatible with the drugs preservative was added (17). No colonies or other evidence of bacterial or fungal growth were detected for any of the formulations tested. There was also no detectable change in color, odor, and taste in any sample. However, in the absence of microbiological data, the

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shelf-life given to extemporaneous products containing preservatives is usually 30 days - the time period in which the formulations were tested.” (page 325, column 2, paragraph 3).

Thus Nahata and Sosnowska teach liquid compositions comprising 1 mg/ml enalapril, a citrate buffer, 0.2% w/w preservative, and water. Although both Nahata and Sosnowska teach the use of a preservative, Nahata and Sosnowska do not teach the use of sodium benzoate as a preservative.

Boukarim is directed towards preservatives in liquid pharmaceutical formulations. Boukarim teaches that sodium benzoate, potassium sorbate, and methyl hydroxybenzoate are commonly used as preservatives in liquid pharmaceutical preparations. Boukarim states, “Among the most commonly used preservatives in the conservation of liquid pharmaceutical preparations are sodium benzoate, potassium sorbate, and methyl hydroxybenzoate (methyl-paraben). Their typical allowed concentrations range respectively from 0.1-0.2%, 0.1-0.2%, and 0.1-0.25% (w/w) (page 14, column 2). Boukarim notes that sodium benzoate is ineffective when formulated at a pH > 5 (page 16, column 2).

The ordinarily skilled artisan would have had a reasonable expectation of success in arriving at the instantly claimed composition in view of the combined teachings of Nahata, Sosnowska, and Boukarim. Nahata and Sosnowska are directed towards liquid formulations of enalapril; both Nahata and Sosnowska teach compositions comprising a) 1 mg/ml enalapril, b) citric acid and/or citrate buffer, c) a preservative, and d) water. Although Nahata and Sosnowska teach methylparaben as a preferred preservative, the ordinarily skilled artisan would recognize methylparaben and sodium benzoate to be functional equivalents in view of the teachings of Boukarim. Boukarim teaches that methylparaben and sodium benzoate are two of the three most common preservatives used for liquid pharmaceutical formulations. As both methylparaben and sodium benzoate are commonly used preservatives known to be suitable for use in liquid formulations, it would be within the purview of the ordinarily skilled artisan to arrive at the instantly

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claimed formulation in view of Boukarim, Nahata, and Sosnowska. In other words, one would find it *prima facie* obvious to substitute the sodium benzoate preservative taught by Boukarim for the methylparaben preservative taught by Nahata and Sosnowska. The Examiner notes that Boukarim particularly teaches the use of sodium benzoate in an amount meeting the instant requirements, and Boukarim explicitly teaches that sodium benzoate is ineffective at a pH > 5. Accordingly, one would find sodium benzoate to be suitable for use in a liquid formulation comprising enalapril, which is ideally at a pH of 3.0. Absent evidence of criticality in the selection of a particular preservative, a particular buffer, or particular amounts of each of the components, optimizing the formulations taught by Nahata and Sosnowska would fall within routine optimization for the ordinarily skilled artisan.

Regarding the limitations directed towards the pH of the formulation, Nahata teaches a citrate buffer having a pH of 5, and an Ora-Sweet/Ora-Plus mixture having a pH of 4.2. Sosnowska also teaches the optimal pH of an enalapril formulation, namely, a pH of 3.0. Thus, Nahata and Sosnowska meet the instant limitations of a formulation having a pH of “about 3 and about 3.5” and “about 3.3” as recited in claims 10, 11, 25, and 26. The use of the word “about” in a claim is appropriate where the claim contains a range of components with no absolute boundaries, and is only limited to the extent that prior art exists which would limit broad interpretation of the claim. See *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1217-1218, 18 USPQ2d 1016 (Fed. Cir. 1991).

Although Nahata and Sosnowska do not explicitly teach that the formulation is stable at about 5 ± 3 °C for at least 12 months, or that the formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period, the combined teachings of Nahata, Sosnowska, and Boukarim meet the instantly claimed requirements, and absent evidence to the contrary, one would expect the composition to have the same properties as instantly claimed. Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior

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art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

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The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-7, 9-22, and 24-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,669,008, herein referred to as '008. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-20 of '008 are generally drawn towards stable oral liquid formulations comprising enalapril, a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Claim 18 is drawn to a particular species of composition, namely, a stable oral liquid formulation, consisting essentially of: (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml sodium benzoate; (v) a flavoring agent; (vi) water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-20 of '008 are drawn to a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-20 of '008.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '008.

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Claims 1-7, 9-22, and 24-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 9,808,442, herein referred to as '442. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-30 of '442 are generally drawn towards methods of treating hypertension, heart failure, and left ventricular dysfunction in a subject, comprising administering a stable oral liquid formulation comprising enalapril; a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-30 of '442 are drawn to methods of use of a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-30 of '442.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '442.

Claims 1-7, 9-22, and 24-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 10,039,745, herein referred to as '745. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-20 of '745 are generally drawn towards stable oral liquid formulations comprising enalapril, a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-20 of '745 are generally drawn towards a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-20 of '745.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '745.

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Claims 1-7, 9-22, and 24-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 10,154,987, herein referred to as '987. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-30 of '987 are generally drawn towards methods of treating hypertension, heart failure, and left ventricular dysfunction in a subject, comprising administering a stable oral liquid formulation comprising enalapril; a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-30 of '987 are drawn to a method of using a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-30 of '987.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '987.

Claims 1-7, 9-22, and 24-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 13-26, and 28-30 of application 16/177,159, herein referred to as '159. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-11, 13-26, and 28-30 of '159 are generally drawn to compositions comprising:

- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer comprising citric acid and sodium citrate;
- (iii) a preservative, wherein the preservative is selected from, *inter alia*, sodium benzoate and benzoic acid; and
- (iv) water.

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The Examiner notes that the buffer of '159, *i.e.*, citric acid and sodium citrate, is the same buffer as recited in instant claims 6, 20-22, and 29-30, and the preservative may be the same preservative recited in the instant claims, *i.e.*, sodium benzoate. The subject matter encompassed by claims 1-11, 13-26, and 28-30 of '159 overlaps with the subject matter encompassed by the instantly claimed invention such that the instant claims are merely an obvious variation of the invention of '159. Accordingly, the instantly claimed invention is not patentably distinct from the invention of claims 1-11, 13-26, and 28-30 of '159.

This is a provisional nonstatutory double patenting rejection.

Conclusion

No claims are allowed in this application.

If applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported *in ipsius verbis*, clarification on the record may be helpful). Should applicants present new claims, applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JEFFREY S LUNDGREN whose telephone number is (571)272-5541. The examiner can normally be reached on Monday through Thursday from 8 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren, can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-270-8380.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stephanie Springer/
Examiner, Art Unit 1629

/JEFFREY S LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 1032
Serial No.: 16/242,898	Examiner: SPRINGER, Stephanie K
Filed: January 8, 2019	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on August 1, 2019, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: _____ /Rose Andico/ Rose Andico</p>

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO THE NON-FINAL OFFICE ACTION DATED MAY 2, 2019

Commissioner:

Applicant hereby submits a response to the Non-Final Office Action dated May 2, 2019 (the “Office Action”), in the above-identified application. Applicant respectfully requests amendment of the patent application, and reconsideration and allowance of the pending claims. The Commissioner is hereby authorized to charge any fees associated with the filing of this response to Deposit Account No. 23-2415, referencing Docket No. 43060-707.305.

Amendments to the Claims, reflecting the status of the claims, begin on page **2**.

Remarks begin on page **6**.

Conclusion begins on page **15**.

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Amendments to the Claims

This listing of claims will replace all prior versions, amendments, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicant reserves the right to pursue the subject matter of the withdrawn claims in this or any other appropriate patent application.

Listing of the Claims:

1. (Original) A stable oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
2. (Original) The stable oral liquid formulation of claim 1 further comprising a sweetener.
3. (Original) The stable oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. (Original) The stable oral liquid formulation of claim 1 further comprising a flavoring agent.
5. (Previously presented) The stable oral liquid formulation of claim 1, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, or a tartrate buffer.
6. (Original) The stable oral liquid formulation of claim 1, wherein the buffer comprises citric acid and sodium citrate.
7. (Original) The stable oral liquid formulation of claim 6, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.
8. (Canceled)

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9. (Original) The stable oral liquid formulation of claim 1, wherein the buffer concentration is about 5 mM to about 20 mM.
10. (Original) The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH between about 3 and about 4.
11. (Original) The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH at about 3.3.
12. (Original) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 18 months.
13. (Original) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 24 months.
14. (Previously presented) A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;wherein the formulation optionally comprises a sweetener and/or a flavoring agent and is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
15. (Previously presented) A stable oral liquid formulation, comprising:
 - (i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below;
 - (iii) about 19% (w/w of solids) of a preservative that is sodium benzoate; and
 - (iv) water;wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and

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wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

16. (Original) The stable oral liquid formulation of claim 15 further comprising a sweetener.
17. (Original) The stable oral liquid formulation of claim 16, wherein the sweetener is sucralose.
18. (Original) The stable oral liquid formulation of claim 15 further comprising a flavoring agent.
19. (Original) The stable oral liquid formulation of claim 15, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, or a tartrate buffer.
20. (Original) The stable oral liquid formulation of claim 15, wherein the buffer comprises citric acid and sodium citrate.
21. (Original) The stable oral liquid formulation of claim 20, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.
22. (Original) The stable oral liquid formulation of claim 15, wherein the buffer comprises citric acid and sodium citrate.
23. (Canceled)
24. (Original) The stable oral liquid formulation of claim 15, wherein the buffer concentration is about 5 mM to about 20 mM.
25. (Original) The stable oral liquid formulation of claim 15, wherein the buffer maintains the pH between about 3 and about 3.5.
26. (Original) The stable oral liquid formulation of claim 15, wherein the buffer maintains the pH at about 3.3.
27. (Original) The stable oral liquid formulation of claim 15, wherein the formulation is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 18 months.
28. (Original) The stable oral liquid formulation of claim 15, wherein the formulation is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 24 months.
29. (Original) A stable oral liquid formulation, comprising:

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(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a citrate buffer to maintain the pH about 4.5 or below comprising citric acid and sodium citrate;

(iii) about 1 mg/ml of a preservative that is sodium benzoate; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

30. (Original) The stable oral liquid formulation of claim 29, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.

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REMARKS

Applicant would like to thank the Office for considering the IDS submitted on February 5, 2019.

Claims 1-7, 9-22, and 24-30 are currently pending in this application. By way of this response, claims 8 and 23 have been canceled. No new matter is presented by way of the amendments.

Withdrawal of any subject matter herein does not constitute an admission that the subject matter is unpatentable for any reason and Applicant reserves the right to file claims directed to withdrawn subject matter in this or a related application.

Election of Species

The Office has required Applicant to “elect a species of buffer to maintain the pH about 4.5 or below, i.e., one of the species recited in paragraph 88 of the specification.”

Applicant made a provisional election, without traverse, during a telephone conversation with the Office on February 27, 2019 to prosecute the buffer species wherein the buffer comprises citric acid and sodium citrate, as recited in claims 6, 7, 20-22, 29 and 30. Applicant hereby affirms the provisional election.

Claims 1-7, 9-22, and 24-30 encompass the elected species.

The §103 Rejection

Claims 1-7, 9-22, and 24-30 are rejected under 35 U.S.C. 103 as obvious over Nahata et al., “Stability of enalapril maleate in three extemporaneously prepared oral liquids,” Am. J. Health-Syst. Pharm., 1998, vol. 55, pages 1155-1157 (cited in IDS) (“Nahata”) in view of Sosnowska et al., “Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared From Commercially Available Tablets,” Acta Poloniae Pharmaceutica - Drug Research, 2009, vol. 66, no. 3, pages 321-326 (cited in PTO-892) (“Sosnowska”) in view of Boukarim et al., “Preservatives in Liquid Pharmaceutical Preparations”, J. Appl. Res., 2009, vol. 9, no. 1&2, pages 14-17 (cited in PTO-892) (“Boukarim”).

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The Office alleges that “both Nahata and Sosnowska teach compositions comprising a) 1 mg/ml enalapril, b) citric acid and/or citrate buffer, c) a preservative, and d) water,” and “[a]lthough Nahata and Sosnowska teach methylparaben as a preferred preservative,” it would be prima facie obvious to substitute methylparaben with sodium benzoate as “Boukarim teaches that methylparaben and sodium benzoate are two of the three most common preservatives used for liquid pharmaceutical formulations.”

Applicant respectfully disagrees.

Applicant respectfully submits that none of the three cited references—Nahata, Sosnowska, and Boukarim—teaches or suggests all the elements of the claimed formulations, e.g., the stability element, that is “the formulation is stable at 5 ± 3 °C for at least 12 months,” is not disclosed or suggested. Such a superior stability is an unexpected result. Applicant further submits an Inventor Declaration by Dr. Gerold Mosher dated February 2, 2017 (the “Mosher Declaration”), with evidence to overcome the §103 rejections asserted by the Office, as discussed in greater detail below.

a. The Cited References Do Not Teach or Suggest Enalapril Oral Liquid Formulations That Are Stable at 5 ± 3 °C For At Least 12 Months

To establish a prima facie case of obviousness, the cited art itself or “the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]” at the time of the invention are to have taught or suggested the claim elements. *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007). The Examiner must make “a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art.” *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995). As such, “obviousness requires a suggestion of all limitations in a claim.” *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

None of Nahata, Sosnowska, and Boukarim teaches or suggests enalapril oral liquid formulations that are stable at 5 ± 3 °C for at least 12 Months, which is one of the elements in the present claims.

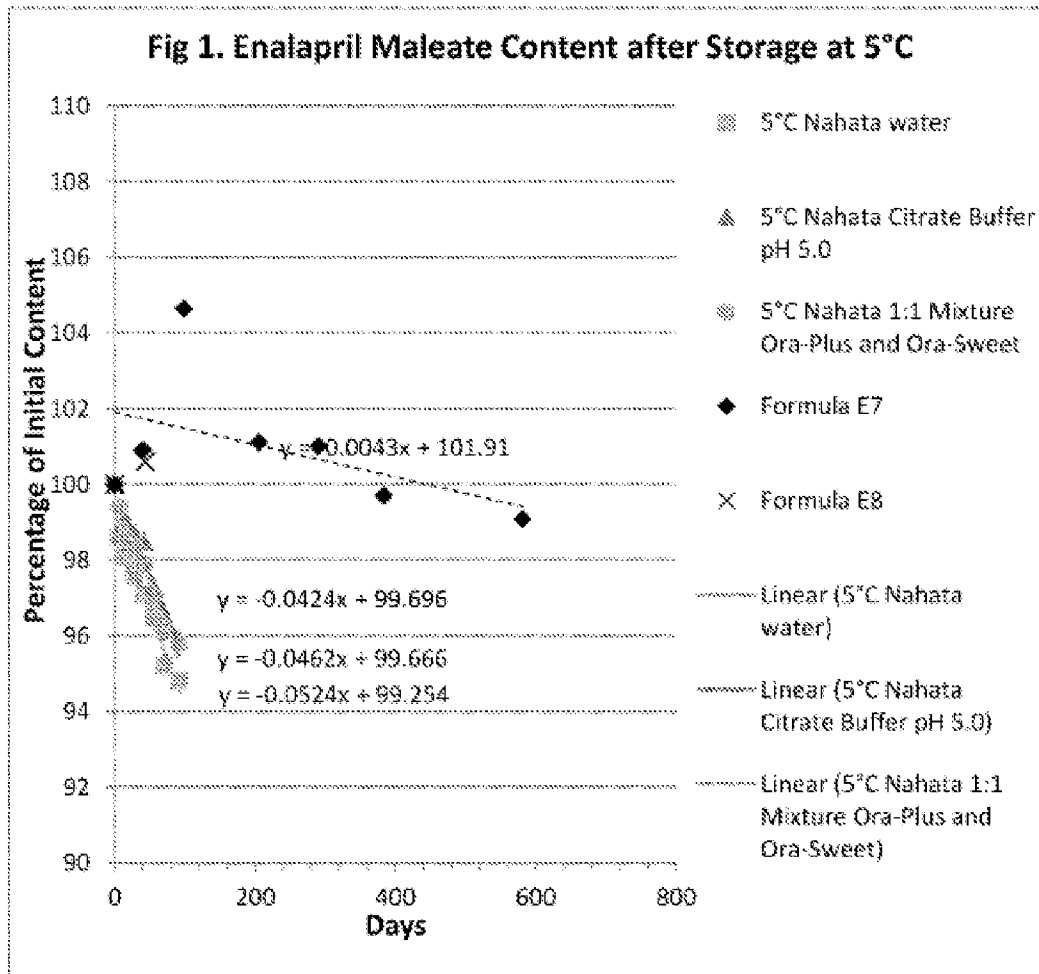
Specifically, claim 1 is directed to a stable oral liquid formulation comprising “(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer to maintain the pH about 4.5 or below; (iii) about 1 mg/ml of a preservative that is sodium benzoate; and (iv) water; **wherein the formulation is stable at about 5 ± 3 °C for at least 12 months**; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.” Claims 14, 15, and 29 similarly recite formulations that comprise the stability element.

The Specification and Drawings of the instant application provide support and evidence of this stability; for example, Table E-2 depicts very little amounts of diketopiperazine or enalaprilat degradants formed in formulations E1 to E6 when stored at 5 °C. Table E-1 shows that formulations E1 to E6 contain enalapril, a buffer (e.g., citric acid and sodium citrate) that maintains the pH at 4.5 or below, a preservative that is sodium benzoate, and water, which Applicant notes are the claimed components of the instant applications.

Moreover, the Mosher Declaration provides additional data supporting the claimed stability by comparing the dramatic differences in stability between the enalapril oral liquid formulations of the present application with the stability of the enalapril liquid preparation in Nahata. In the Mosher Declaration, Dr. Mosher plotted graphically with linear regression of the data for extrapolation of the available refrigerated (5 °C) and room temperature (25 °C) stability data published by Nahata as well as E7 and E8 enalapril formulations, which are exemplary formulations of the present application. The stability comparisons at 5 °C are presented in Fig 1. as below:

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As Dr. Mosher explains, “Table A and Fig. 1 show that E7 exhibits excellent stability for at least 18 months (581 days) at 5 °C with essentially no loss of enalapril content in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at 5 °C for more than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.” Mosher Declaration, ¶21. Evidently, a stability of at least 12 months at 5 ± 3 °C is not an inherent property of the Nahata formulations.

Sosnowska similarly discloses extemporaneously prepared formulations. As the Office has noticed, “Sosnowska teaches liquid formulations of enalapril, **prepared from crushed enalapril tablets** ... in the absence of microbiological data, the shelf-life given to extemporaneous products containing preservatives is usually 30 days - the time period in which

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the formulations were tested.” Sosnowska does not disclose or suggest a stability beyond 30 days for the extemporaneous preparations. *See, e.g.*, Table 1 of Sosnowska.

Further, Applicant respectfully points out that the instant application is directed to novel stable enalapril oral liquid formulations with superior stability and uniformity properties. As Dr. Mosher explains, the “currently approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in “Nahata” and subsequently administering the suspension to the patient, or (3) reconstituting a powder in a liquid carrier” and “[f]or the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination.” Mosher Declaration, ¶10-11. The stable enalapril oral liquid formulations in the present application represent an elegant solution over the previous methods of obtaining liquid enalapril formulation.

Thus, the data presented in the Mosher Declaration clearly demonstrates that extemporaneous preparations, such as the preparations disclosed in Nahata and Sosnowska, do not meet the stability requirement of the present claims.

As such, none of the cited references—Nahata, Sosnowska, and Boukarim—discloses or suggests any liquid formulations of enalapril having a stability **at about 5 ± 3 °C for at least 12 months**, either explicitly or by inherency. Accordingly, Applicant respectfully requests the §103 rejections be withdrawn.

b. The Cited References Provide No Reasonable Expectation of Success of the Claimed Subject Matter

Obviousness does not require absolute predictability; however, at least some degree of predictability is required. MPEP § 2143.02. To have a reasonable expectation of success, one must be motivated to do more than merely “vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of

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which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *Medichem, S.A. v. Robaldo*, 327 F.3d 1157, 1165 (Fed. Cir. 2006).

There is no expectation from Nahata or Sosnowska that the extemporaneously prepared oral liquid formulation can be modified to have a stability at about 5 ± 3 °C for at least 12 months. In fact, as Dr. Mosher explains, “the extrapolated lines [in Nahata] show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.” Mosher Declaration, ¶12. Thus, one of ordinary skill in the art would not reasonably expect, based on the teachings in Nahata, to make a formulation having a stability at about 5 ± 3 °C for a period of time that is more than three times longer than the Nahata formulation.

Similarly, Sosnowska does not show any stability data beyond 30 days. When stored at 4 °C, Sosnowska formulations with an initial enalapril concentration at about 1.0 mg/mL contained only about 98% initial enalapril concentration at the end of the 30-day period. One of ordinary skill in the art would not reasonably expect, based on the teachings in Sosnowska, to make a formulation having a stability at about 5 ± 3 °C for a period of time that is more than 12 times longer than the Sosnowska formulations, when a stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

Thus, the Office has not established how one of skill in the art would expect to modify the extemporaneously prepared formulations in Nahata or Sosnowska and to arrive at a stable oral liquid formation meeting all the elements of the present claims.

Further, the enalapril tablets used in the extemporaneous preparations of Nahata contain, in addition to enalapril, lactose, magnesium stearate, sodium bicarbonate, starch, and iron oxide. Ora-Plus is an oral suspending vehicle that has a pH of approximately 4.2 and that contains purified water, microcrystalline cellulose, sodium carboxymethylcellulose, xanthan gum, carrageenan, buffering agents (trisodium phosphate and citric acid), an antifoaming agent (simethicone), and preservatives (potassium sorbate and methylparaben). Ora-Sweet syrup vehicle is a flavoring vehicle that is buffered to a pH of approximately 4.2 and that contains purified water, sucrose, glycerin, sorbitol (5%), flavoring, buffering agents (sodium phosphate

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and citric acid), and preservatives (potassium sorbate and methylparaben). Nahata therefore teaches that these extemporaneously prepared suspensions from enalapril tablets contain a myriad of components, the majority of which are not present in the presently claimed formulations. The following table lists the components that are present in the Nahata formulation:

Enalapril Extemporaneous Formulation (Ora-Sweet/Ora-Plus)
Enalapril
Lactose
magnesium stearate
sodium bicarbonate
Starch
iron oxide
microcrystalline cellulose
carboxymethylcellulose
xanthan gum
carrageenan
calcium sulphate
trisodium phosphate
citric acid
dimethicone
potassium sorbate
methylparaben
Flavoring
Sorbitol
Glycerin
sucrose
Water

Apparently, the extemporaneously prepared formulation in Nahata contains 19 components in addition to enalapril and water. As such, Nahata does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations, which can extend the stability from less than 100 days to at least 12 months at 5 °C. One of skill in the art would need to consider all of these excipients and, through trial-and-error, determine whether each and every one of these components is necessary for stability or if they could be varied or eliminated.

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In addition, Sosnowska teaches formulations containing a raspberry syrup, methyl hydroxybenzoate as preservative, a citrate buffer, and hydroxyethylcellulose as a suspending agent. Sosnowska does not provide any expectation or suggestion that any modification of the components can lead to a stable oral liquid formulation that is stable at about 5 ± 3 °C for at least 12 months (that is 12 times longer than the stability period shown in Sosnowska).

Thus, the Office has not demonstrated a reasonable expectation of success based on Nahata or Sosnowska.

c. Unexpected Results

Applicant submits that the subject matter in the claims has unexpected results with respect to stability of liquid enalapril formulations.

As explained in the Mosher Declaration, the claimed stable enalapril liquid formulations are dramatically much more stable than extemporaneously prepared enalapril formulations. In the Mosher Declaration, Dr. Mosher plotted graphically, with linear regression of the data for extrapolation of the stability data published in Nahata, as well as corresponding E7 and E8 enalapril formulations, which are exemplary formulations of the present claims. *See*, Mosher Declaration, Fig 1 and Fig 2.

As evidenced by the graphs, the E7 formulation demonstrates no loss of enalapril for at least 12 months at 5 °C and about 100 days at 25 °C. The E8 formulation, which has only one data point, is expected to trend similarly. These results drastically contrast with the stability or lack thereof in the extemporaneous enalapril preparations, where the enalapril degrades substantially after initial preparation. At about 90-100 days, the extemporaneous preparations are at about 95% of the starting enalapril concentration when stored at either 4 °C or 25 °C.

The unexpected stability results of the E7 and E8 formulations are not taught by, and could not have been predicted or contemplated by Nahata, Sosnowska, or Boukarim.

Accordingly, Applicant respectfully requests the §103 rejection be withdrawn.

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Double Patenting Objection

Claims 1-7, 9-22, and 24-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,669,008, claims 1-30 of U.S. Patent No. 9,808,442, claims 1-20 of U.S. Patent No. 10,039,745, and claims 1-30 of U.S. Patent No. 10,154,987.

Without acquiescing in this ground of rejection and solely in an effort to expedite prosecution, Applicant hereby submits Terminal Disclaimers with respect to U.S. Patent No. 9,669,008, U.S. Patent No. 9,808,442, U.S. Patent No. 10,039,745, and U.S. Patent No. 10,154,987.

Claims 1-7, 9-22, and 24-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 13-26, and 28-30 of U.S. Patent Application No. 16/177,159.

Without acquiescing in this ground of rejection and solely in an effort to expedite prosecution, Applicant hereby submits a Terminal Disclaimer with respect to U.S. Patent Application No. 16/177,159.

The Terminal Disclaimers obviate the present rejections. Accordingly, Applicant respectfully requests that the rejections be withdrawn.

In view of the remarks and amendments submitted herein, Applicant believes that the Application is in condition for allowance and such action is earnestly solicited.

* * *

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CONCLUSION

Applicant submits that this response fully addresses the Office Action dated May 2, 2019. Applicant believes that for the reasons set forth herein the pending claims are in condition for allowance and early and favorable consideration is respectfully requested.

Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (617) 598-7823.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: August 1, 2019

By: /Clark Lin/
Clark Y. Lin, Ph.D., Esq.
Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (617) 598-7823
Customer No. 021971

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed		PTO/SB/25 PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce
Electronic Petition Request	TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	
Application Number	16242898	
Filing Date	08-Jan-2019	
First Named Inventor	Gerold MOSHER	
Attorney Docket Number	43060-707.305	
Title of Invention	ENALAPRIL FORMULATIONS	
<input checked="" type="checkbox"/> Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action <input checked="" type="checkbox"/> This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.		
Owner	Percent Interest	
Silvergate Pharmaceuticals, Inc.	100 %	
The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)		
16177159 filed on 10/31/2018 as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns. In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.		
The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)		

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as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

☐ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

- ☐ Small Entity
- ☐ Micro Entity
- ☒ Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

☒ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 67024

☐ A sole inventor

☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

☐ A joint inventor; all of whom are signing this request

Signature	/Clark Lin/
Name	Clark Y. Lin

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Doc Code: DISQ.E.FILE

Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16242898

Filing Date: 08-Jan-2019

Applicant/Patent under Reexamination: MOSHER

Electronic Terminal Disclaimer filed on August 1, 2019

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Examiner: Stephanie K. Springer
Serial No.: 15/081,603	Confirmation No.: 3892
Filed: March 25, 2016	Customer No.: 021971
Title: ENALAPRIL FORMULATIONS	

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132

I, **Gerold Mosher**, do hereby declare as follows:

1. I am currently employed at Silvergate Pharmaceuticals, Inc.
2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.
3. I have been employed at Silvergate Pharmaceuticals since 2013, as Vice President of Drug Development. As part of my job duties, I develop oral solutions for pediatric use. I have a small laboratory where I develop, characterize and move formulations through the steps required for FDA approval and eventual sale.
4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also

been employed by small startup companies to develop new solubilizing technology for oral, injectable and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for almost 38 years, and have extensive experience in developing pharmaceutical formulations. My Curriculum Vitae is attached as Exhibit A.

6. I am familiar with the subject matter claimed in patent application 15/081,603, and am a named inventor on this application. Silvergate Pharmaceuticals is also the Assignee of the '603 application.

7. I am aware of the Non-Final Office Action mailed in this matter on January 17, 2017. I am also aware that the oral enalapril liquid formulation claims stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over US 8,568,747, Nahata et al. (Stability of Enalapril Maleate in three Extemporaneously Prepared Oral Liquids) ("Nahata"), Product Information of Bicitra (Sodium Citrate and Citric Acid Oral Solution) ("Bicitra"), Product Information of Ora-Sweet ("Ora-sweet"), and Rippley et al. (Pharmacokinetics Assessment of an Oral Enalapril Suspension for Use in Children) ("Rippley"). I have reviewed these cited references in the Non-Final Office Action.

8. I am submitting this declaration to address the comments made in the Office Action.

9. The '603 application relates to enalapril oral liquid formulations that are stable for least 12 months at 5 ± 3 °C. The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water at a pH of less than 3.5. Development of this described enalapril formulation was oriented on preparing a safe, stable, soluble oral liquid with minimal degradation and having acceptable taste for pediatric patients.

10. The currently approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in "Nahata" and subsequently administering the suspension to the

patient, or (3) reconstituting a powder in a liquid carrier, such as the described enalapril powder in US 8,568,747.

11. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty in swallowing oral dosage forms. For the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination. Similarly, reconstituting powders into a liquid carrier also requires an extra step and could introduce variability, solubility and contamination issues during the reconstitution.

12. As compared to these currently available methods, the enalapril oral liquid formulations claimed in the '603 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

13. It should be appreciated that the oral enalapril liquid formulations of the present claims are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

14. Evidence of this stability is found in exemplary formulations E7 and E8 which show minimal degradation as compared to current formulations. In this study, exemplary formulations E7 and E8 were stored at either refrigerated condition (5 °C) or at ambient condition (25 °C). Formulations details for E7 and E8 are as follows:

Composition of Enalapril Maleate Formulations		
Component	E7	E8
Enalapril maleate	1.00	1.00
Citric acid anhydrous	1.80	1.82
Sodium citrate anhydrous	0.16	0.15
Sodium benzoate	1.00	1.00
Sucralose	0.70	0.70
Mixed berry flavor	0.50	0.50
Water	qs	qs
pH (measured)	3.3	3.3

qs = sufficient quantity

15. In my review of the references cited in the Office Action, none of the references describe this stability of at least 12 months at 5 ± 3 °C or any means of achieving this stability for enalapril formulations.

16. I have reviewed Nahata which describes the extemporaneous preparation of oral liquid enalapril formulations by crushing enalapril tablets with a mortar and pestle and suspending the resulting ground tablets in water, citrate buffer, or Ora-Plus/Ora-Sweet. On stability, Nahata states that the “compounded oral liquids [were] stable for 91 days at 4 and 25 °C” defining stable as “concentration after storage was $\geq 90\%$ of the initial concentration. Table 1 of Nahata shows that the enalapril extemporaneous formulations exhibited about 5% loss of enalapril after about 56 days at 4 °C and about 5% loss of enalapril after about 91 days at 25 °C.

17. I have also reviewed US 8,568,747 which describes an oral liquid enalapril formulation obtained by reconstituting an enalapril powder in a liquid. The table in example 6 of US 8,568,747 shows that the resulting oral liquid formulation exhibited about 5% loss of enalapril after about 8 weeks at 25 °C.

18. I additionally reviewed Bicitra, Ora-sweet, and Rippley and they do not provide any stability of enalapril formulations whatsoever.

19. To compare the stability of the enalapril extemporaneous preparations as described in Nahata and the reconstituted liquid formulation of US 8,568,747, I submit the following data which depicts the enalapril content of formulations E7 at 5 °C and 25 °C and E8 at 5 °C in Table A and Table B:

Table A: Enalapril content in formulations after storage at 5 °C¹

Days	Nahata			E7	E8
	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet		
0	100	100	100	100	100
7	98.6	98.7	99.4		
14	98.1	99.1	98.6		
28	97.6	98.7	98.4		
40				100.9	
42	97.1	98.5	97.9		100.3
56	96.5	97.3	96.9		
70	95.2	96.3	96.1		
91	94.8	95.9	95.8		
99				104.7	
205				101.1	
290				101.0	
383				99.7	
581				99.1	

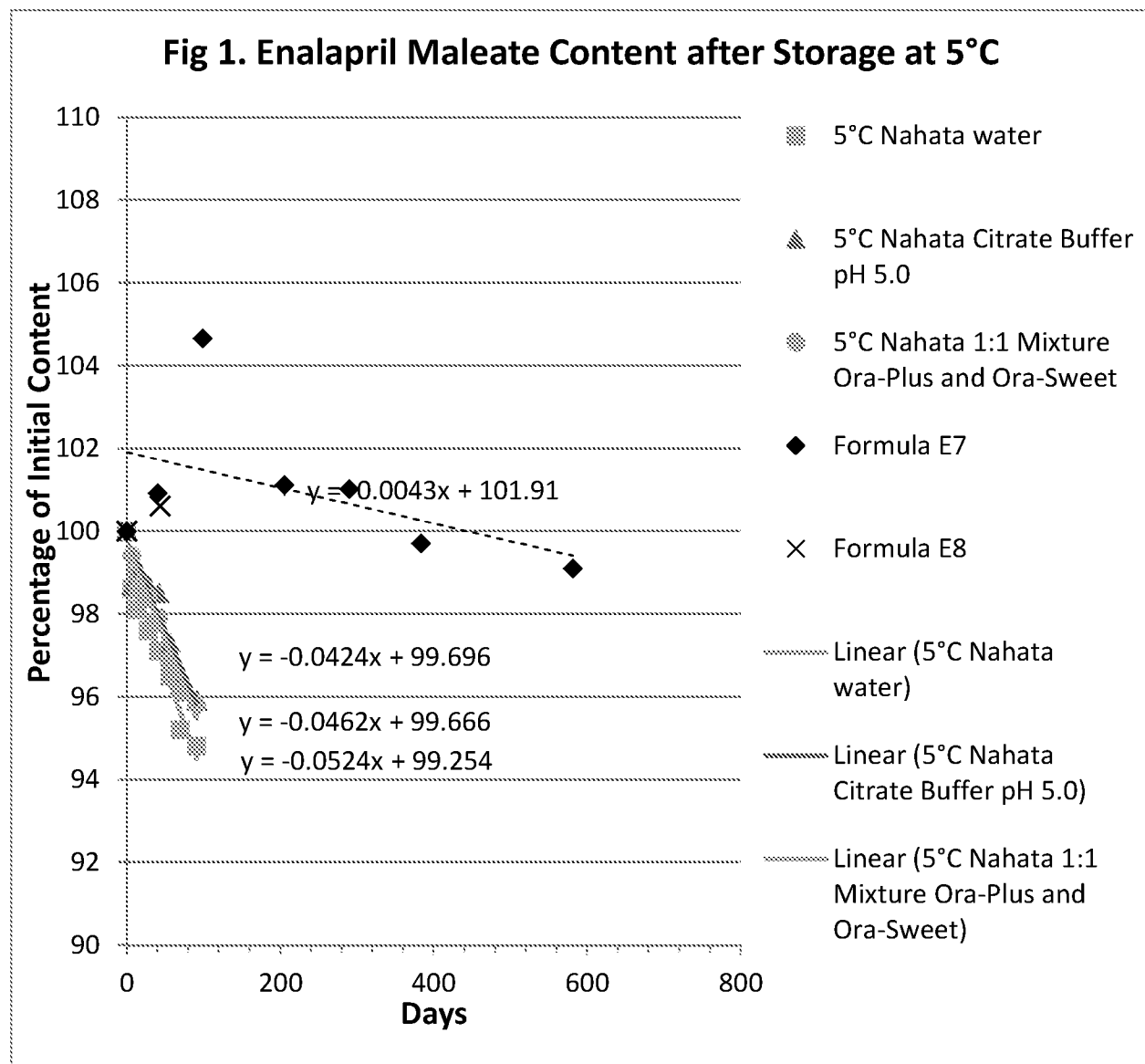
Table B: Enalapril content in formulations after storage at 25 °C

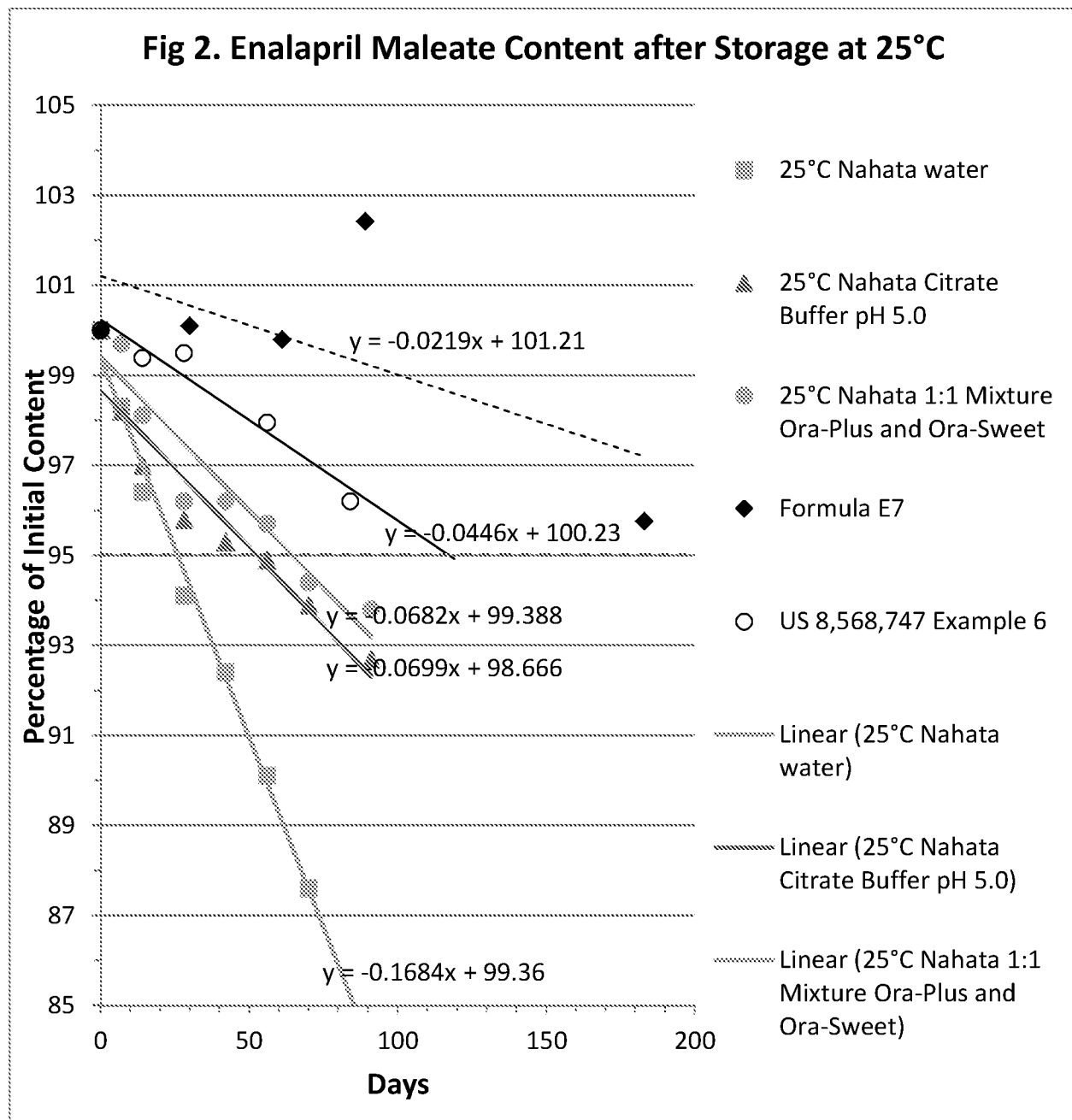
Days	Nahata			US 8,568,747	E7
	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	Example 6	
0	100	100	100	100	100
7	98.3	98.2	99.7		
14	96.4	97	98.1	99.4	
28	94.1	95.8	96.2	99.5	
30					100.1
42	92.4	95.3	96.2		
56	90.1	94.9	95.7	97.9	
61					99.8

¹ I note that US 8,568,747 does not provide stability data of the reconstituted liquid formulation at 5 °C.

70	87.6	93.9	94.4		
84				96.2	
89					102.4
91	84.1	92.7	93.8		
183					95.8

20. To further describe the contrast in stability, the enalapril concentrations published by Nahata, the US 8,568,747 enalapril concentrations, and the concentrations from E7 and E8 are plotted graphically (Fig. 1: 5 °C and Fig. 2: 25 °C) with linear regression of the data for extrapolation.





21. Table A and Fig. 1 show that E7 exhibits excellent stability for at least 18 months (581 days) at 5 °C with essentially no loss of enalapril content in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at 5 °C for more than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.

22. Table B and Fig. 2 show that E7 also exhibits better stability for at least 6 months (183 days) at 25 °C in contrast to the Nahata preparations and the reconstituted formulation of US 8,568,747.

23. The additional enalapril content data submitted for E7 and E8 shows that the formulations of the present application are significantly more stable, which in my opinion reflects the superior results and advantages, obtained with the oral liquid enalapril formulation of the present claims.

24. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under 18 U.S.C. 1001.

Respectfully submitted on this 2nd day of February, 2017

A handwritten signature in cursive script, appearing to read "Gerold L. Mosher", is written over a horizontal line.

Gerold L. Mosher, Ph.D.

ADDRESSES

Silvergate Pharmaceuticals, Inc.
 7300 West 110th Street, Suite 950
 Overland Park, KS 66210
 (913) 424-9294
 Jerry.mosher@silvergatepharma.com

Home
 12215 Avila Drive
 Kansas City, MO 64145
 Mobile (913) 424-9294
 jerry@coweemosher.com

EDUCATION

Ph.D., Pharmaceutical Chemistry (1986) University of Kansas, Lawrence, KS
 MS, Pharmaceutical Chemistry (1984) University of Kansas, Lawrence, KS
 BS, Pharmacy (1979) University of Kansas, Lawrence, KS

PROFESSIONAL EXPERIENCE

SILVERGATE PHARMACEUTICALS, INC (2013-Present)

Vice President of Drug Development

VERROW PHARMACEUTICALS, INC., Lenexa, KS (2008-present)

Scientific Advisor (2013-present)

Chief Scientific Officer and Vice President of Product Development (2008-2013)

CYDEX PHARMACEUTICALS, INC., Overland Park, KS (1998-2008)

Sr. Director, Product Development

UNIVERSITY OF MISSOURI-KANSAS CITY, Kansas City, MO (1996-1998)

Research Associate Professor, Division of Pharmaceutical Science (1996-1998)

Associate Director of the Center for Pharmaceutical Technology (1996-1998)

MIDWEST RESEARCH INSTITUTE, Kansas City, MO (1995-1996)

Manager, Pharmaceutical Product Development Section (1996)

Senior Chemist, Formulations Group Leader (1995)

INTERx DIVISION OF MERCK & COMPANY, Lawrence, KS (1992-1995)

Research Fellow

ELI LILLY & COMPANY, Indianapolis, IN (1986-1992)

Research Scientist (1990-1992)

Senior Pharmaceutical Chemist (1986-1990)

ST. JOSEPH HOSPITAL, Concordia, Kansas (1979-1981)

Staff Pharmacist

MEMBERSHIPS

American Association of Pharmaceutical Scientists (AAPS)

Phi Lambda Upsilon Honorary Chemical Society

Sigma XI

PATENTS (US only)

GL Mosher and DW Miles, Unpublished patent application, filed 2015, Patent Pending

GL Mosher and DW Miles, Unpublished patent application, filed 2015, Patent Pending

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. Publication 2016/0058786, Patent Pending.

JD Pipkin, GL Mosher and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. Publication 2015/0050355, Patent Pending.

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. US Patent 9,125,945 (2015).

GL Mosher, SG Machatha and DJ Cushing, Pharmaceutical Compositions Comprising Prasugrel and Cyclodextrin Derivatives and Methods of Making and Using the Same. Publication 2015/0005341, Patent Pending.

GL Mosher, Stabilized Formulation Containing Iodinated Contrast Agents and Cyclodextrins. Publication 2014/0377185, Patent Pending.

GL Mosher, Stabilized Formulation Containing Iodinated Contrast Agents and Cyclodextrins. Publication 2013/0323181, Patent Pending.

JD Pipkin, RO Zimmerer, DO Thompson and GL Mosher, Inhalant Formulation Containing Sulfoalkyl Ether Cyclodextrin and Corticosteroid. Publication 2013/0303498, Patent Pending.

JD Pipkin, RO Zimmerer, DO Thompson and GL Mosher, Inhalant Formulation Containing Sulfoalkyl Ether Cyclodextrin and Corticosteroid. Publication 2013/0059826, Patent Pending.

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. US Patent 8,853,236 (2014).

GL Mosher, JD Pipkin and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 8,846,901 (2014).

GL Mosher, SG Machatha and DJ Cushing, Pharmaceutical Compositions Comprising Prasugrel and Cyclodextrin Derivatives and Methods of Making and Using the Same. US Patent 8,835,407 (2014).

JD Pipkin, GL Mosher and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 8,829,182 (2014).

JD Pipkin, GL Mosher and DB Hecker, DPI Formulation Containing Sulfoalkyl Ether Cyclodextrin. Publication 2013/0197105, Patent Pending.

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. US Patent 8,343,995 (2013).

JD Pipkin, GL Mosher and DB Hecker, DPI Formulation Containing Sulfoalkyl Ether Cyclodextrin. Publication 2012/0164184, Patent Pending.

GL Mosher, SG Machatha and DJ Cushing, Pharmaceutical Compositions Comprising Prasugrel and Cyclodextrin Derivatives and Methods of Making and Using the Same. US Patent 8,236,782 (2012).

JD Pipkin, GL Mosher and DB Hecker, DPI Formulation Containing Sulfoalkyl Ether Cyclodextrin. US Patent 8,114,438 (2012).

GL Mosher, JD Pipkin and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 8,049,003 (2011).

JD Pipkin, GL Mosher and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 7,629,331 (2009).

DO Thompson and GL Mosher, Formulations Containing Propofol and a Sulfoalkyl Ether Cyclodextrin. US Patent 7,034,013 (2006).

GL Mosher, KT Johnson, AA Gayed, and DO Thompson, Formulations Containing Amiodarone and a Sulfoalkyl Ether Cyclodextrin. US Patent 6,869,939 (2005).

VJ Stella, RA Rajewski, MR Venkatramana, JW McGinity, and GL Mosher, Sulfoalkyl Ether

Cyclodextrin Based Controlled Release Solid Pharmaceutical Formulations. US Patent 6,046,177 (2000).

GL Mosher, Absorption Enhancer/Solubilizer Combination for Improved Bioavailability of a Zwitterionic Compound. US Patent 5,525,596 (1996).

GL Mosher and MV Mullen, R-Forms of Cefuroxime Axetil. US Patent 5,063,224 (1991).

PUBLICATIONS

Elizabeth S. Rowe, Vernon D. Rowe, Sangita Biswas, Gerold Mosher, Lovella Insisienmay, Marlies K. Ozias, Michael R. Gralinski, John Hunter, James S Barnett, (2016) Preclinical Studies of Kidney Safe Iodinated Contrast Agent, J. Neuroimaging, May 12, 2016 online.

D Cushing, P Souney, W Cooper, G Mosher, M Adams, S Machatha, B Zhang, and P Kowey, Assessment of the pharmacokinetics and platelet aggregation inhibitory effects of a novel intravenous formulation of clopidogrel in humans, Clin. Exp. Pharm. Physiol., 39: 3-8 (2012).

GL Mosher, VD Antle, and JD Pipkin, Sulfobutylether β -Cyclodextrin, in Handbook of Pharmaceutical Excipients, 7th Edition by Rowe, R.C., Sheskey, P.J. Cook, W.G., and Fenton, M.E., Eds, London:Pharmaceutical Press, 823-826 (2012).

GL Mosher and SG Machatha, Complexation: Cyclodextrins, in Encyclopedia of Pharmaceutical Science and Technology, 4th Edition by Swarbrick, J., New York: Informa Healthcare USA Inc., (2013).

GL Mosher and JD Pipkin, Sulfobutyl Ether β -Cyclodextrin, in Handbook of Pharmaceutical Excipients, 6th Edition by Rowe, R.C., Sheskey, P.J. and Quinn, M.E, Eds, London: Pharmaceutical Press, 714-717 (2009).

GL Mosher and JD Pipkin, Sulfobutyl Ether β -Cyclodextrin, in Handbook of Pharmaceutical Excipients, 5th Edition by Rowe, R.C., Sheskey, P.J. and Owen S.C, Eds, London: Pharmaceutical Press, 754-757 (2006).

G Mosher and DO Thompson, Complexation: Cyclodextrins, in Encyclopedia of Pharmaceutical Technology: Third Edition by Swarbrick, J., New York: Informa Healthcare USA Inc., Volume 2, 671-696 (2006).

GL Mosher and JD Pipkin, Sulfobutyl Ether β -Cyclodextrin, in Pharmaceutical Excipients 2004 by Rowe, R.C., Sheskey, P.J. and Owen S.C, Eds, London: Pharmaceutical Press (2004).

SF Lockwood, S O'Malley and GL Mosher, Improved aqueous solubility of crystalline astaxanthin (3,3'-dihydroxy- β , β -carotene-4,4'-dione) by Captisol[®] (sulfobutyl ether β -cyclodextrin), J. Pharm. Sci., 92(4): 922-926 (2003).

GL Mosher and DO Thompson, Complexation and Cyclodextrins, in Encyclopedia of Pharmaceutical Technology by Swarbrick, J. and Boylan, J.C., New York: Marcel Dekker, Inc., Volume 19, 49-88 (2000).

GL Mosher, The determination of interfacial transfer constants using side-by-side diffusion cells, Pharm. Res., 11(9): 1325-1329 (1994).

GL Mosher, J McBee and DB Shaw, Esterase activity towards the diastereomers of cefuroxime axetil in the rat and dog, Pharm. Res., 19(5): 687-689 (1992).

GL Mosher and J McBee, Photoreactivity of LY277359 maleate, a 5-HT₃ receptor antagonist, in solution, Pharm. Res., 8(10): 1215-1222 (1991).

GL Mosher, H Bundgaard, E Falch, C Larsen, and T Mikkelsen, Ocular bioavailability of pilocarpic acid mono- and diester prodrugs as assessed by miotic activity in the rabbit, Int. J. Pharm., 39: 113-120 (1987).

H Bundgaard, E Falch, C Larsen, GL Mosher and T Mikkelsen, Pilocarpine prodrugs. II. Synthesis, stability, bioconversion, and physicochemical properties of sequentially labile pilocarpic acid diesters, J. Pharm. Sci., 75: 775-783 (1986).

GL Mosher, Theoretical and Experimental Evaluation of Pilocarpine Prodrugs for Ocular Delivery, Dissertation for Doctor of Philosophy, (1986).

GL Mosher, Diethylpropion, a monograph in Chemical Stability of Pharmaceuticals by Connors, Amidon, Kennon and Stella, 2nd Edition, New York: John Wiley and Sons, (1986).

H Bundgaard, E Falch, C Larsen GL Mosher and T Mikkelsen, Pilocarpic acid esters as novel sequentially labile pilocarpine prodrugs for improved ocular delivery, J. Med. Chem., 28: 979-781 (1985).

GL Mosher and TJ Mikkelsen, Permeability of the n-alkyl p-aminobenzoate esters across the isolated corneal membrane of the rabbit, Int. J. Pharm., 2: 239 (1979).

ABSTRACTS/PRESENTATIONS

S Biswas, ES Rowe, G Mosher, MK Ozias, MR Gralinski, and VD Rowe, Veropaque, A Novel Contrast Formulation, Mitigates Contrast Induced Acute Kidney Injury, 24th Annual Transcatheter Cardiovascular Therapeutics Meeting, Miami, FL (Nov 22-26, 2012). Abstract in J Am Coll Cardiol 60(17) Suppl. B :B40 (2012).

JD Pipkin, SG Machatha, GL Mosher, and Q He, Bioequivalence of a Captisol-Enabled[®] fosphenytoin sodium injection formulation to the marketed reference listed product via IV and IM administration in healthy volunteers, 64th Annual Meeting of the American Epilepsy Society, San Antonio, TX (Dec 3-7, 2010).

SG Machatha, C Fulk, GL Mosher and JD Pipkin, The effects of Captisol[®] on the solubilization and stabilization of antiepileptic drugs, 2010 AAPS Annual Meeting and Exposition, New Orleans, LA (Nov 14-18, 2010).

S Biswas, ES Rowe, G Mosher, L Tejada, MK Ozias, and VD Rowe, Nephroprotective effects of substituted cyclodextrins, 15th International Cyclodextrin Symposium, Vienna Austria, (May 9-12, 2010).

SG Machatha, GL Mosher and DJ Cushing, Effects of modified cyclodextrin derivatives on the solubility and stability of prasugrel in aqueous formulations, 2009 AAPS Annual Meeting and Exposition, Los Angeles, CA (Nov 8-12, 2009).

PF Souney, J Cowee, DJ Cushing, G Mosher, and P Holmes, Stability of a cyclodextrin-based IV formulation of amiodarone when diluted with 5 percent dextrose or 0.9 percent sodium chloride injections in both PVC and polyolefin intravenous bags over 7 days, 2009 ASHP Summer Meeting, Rosemont, IL (June 14-17, 2009).

D Cushing, R Lipicky, P Kowey, C Cannon, M Adams, W Cooper and G Mosher, Assessment of the pharmacokinetic and pharmacodynamic effects of intravenous clopidogrel in humans, American College of Cardiology 58th Annual Scientific Session, Orlando, FL (Mar 28-31, 2009).

PF Souney, J Cowee, G Mosher and DJ Cushing, Stability of intravenous amiodarone formulations in glass, polyolefin and polyvinylchloride containers over 72 hours, ASHP Midyear Clinical Meeting, Orlando, FL (Dec 7-11, 2008).

SG Machatha, RL Wedel, KT Johnson and GL Mosher, Effects of modified cyclodextrin derivatives on the solubility and stability of clopidogrel bisulfate in aqueous formulations, 2007 AAPS Annual Meeting and Exposition, San Diego, CA (Nov 10-15, 2007).

PW Holmes, SG Machatha, CF Fulk and GL Mosher, The common ion effect and its impact on the development of a stable Captisol-Enabled[®] fosphenytoin sodium injection formulation, 2007 AAPS

Annual Meeting and Exposition, San Diego, CA (Nov 10-15, 2007).

DJ Cushing, WD Cooper, GL Mosher, MR Gralinski and BW Massey, Pharmacokinetic and pharmacodynamic effects of a novel intravenous formulation of clopidogrel bisulfate, 2007 AAPS Annual Meeting and Exposition, San Diego, CA (Nov 10-15, 2007).

G Mosher, Clinical pharmacokinetics and taste assessment comparison of an aqueous sulfobutylether- β -cyclodextrin based oral formulation of sertraline HCl to Zoloft oral concentrate, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

KT Johnson and G Mosher, Investigation of atypical bi-phasic complexation curves observed when charged cyclodextrins solubilize charged drug compounds, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

R Wedel, A Gayed and GL Mosher, Development of an aqueous-based oral solution formulation of sertraline HCl using sulfobutylether- β -cyclodextrin, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

CF Fulk, A Gayed, B Lund, GL Mosher, DO Thompson and R Wedel, Preserved formulations containing Captisol[®] brand of sulfobutylether- β -cyclodextrin, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

SJ Carter, DA Robaugh, RO Zimmerer, GL Mosher and NJ Cogburn, Overcoming unique challenges in developing a method for the quantitation of sulfobutyl ether β -cyclodextrin in rat and dog plasma by LC/MS, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

S Katpally, MK Ghorab, D Thompson, G Mosher, JD Madura and MC Adeyeye, Characterization of bile salt / SBE7- β -cyclodextrin interactions using isothermal titration calorimetry, 2002 AAPS Annual Meeting and Exposition, Montreal Canada (Nov 10-14, 2002).

ML Sirna, CF Fulk, and GL Mosher, Captisol-Enabled[™] Propofol: Formulation approaches to reduce oxidation, 2002 AAPS Annual Meeting and Exposition, Montreal Canada (Nov 10-14, 2002).

A Vargas-Perex, S Katpally, A Jain, G Mosher, D Thompson and MC Adeyeye, Complexation characteristics of sulfobutylether 7- β -cyclodextrin (SBE7-CD) with chenodeoxycholic acid, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

S Katpally, A Vargas-Perez, D Thompson, G Mosher and MC Adeyeye, Complexation characteristics of sulfobutylether- β -cyclodextrin (SBE7-CD) with bile acids, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

KT Johnson and G Mosher, Development and qualification of a fluorescence method for the determination of sulfobutylether-7- β -cyclodextrin delivered in an aerosol inhalation safety study, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

G Mosher, and C Fulk, Co-solvent effects on the rate and extent of solubilization of drugs by Captisol[®] brand of sulfobutyl ether β -cyclodextrin, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

CA Vasquez, NA Neilan and GL Mosher, In vitro evaluation of biocompatibility of a dose formulation, 40th Annual Meeting of the Society of Toxicology, San Francisco, CA, (Mar 25-29, 2001).

C Fulk, SM Ghate, GL Mosher and DO Thompson, Preparation of the ammonium salt of sulfobutyl ether β -cyclodextrin (Captisol[®]) for use in controlled release formulations, 27th International Symposium on Controlled Release of Bioactive Materials, Paris, (July 7-13, 2000).

GL Mosher, Cyclodextrins, they're not just for breakfast any more, Kansas City Discussion Group of Pharmaceutical and Allied Scientists, (Jan 2000).

GL Mosher, S Bradley and E Evans, Continuous IV infusion studies in dogs, Kansas City Discussion Group of Pharmaceutical and Allied Scientists, (1996).

GL Mosher, K Trubitt-Johnson and RC Wood, Absorption enhancer solubilizer combination for improved bioavailability of a zwitterionic compound, 9th Annual AAPS National Meeting, (1994).

SA Sweetana and GL Mosher, Bile salt-insulin interactions. Optical spectroscopy studies. 6th Annual AAPS National Meeting, (1991).

J McBee and GL Mosher, Hydrolysis of four dihydrolysergic acid derivatives using in vitro enzyme systems from the rat and dog, 3rd Annual AAPS National Meeting, (1989).

GL Mosher and T Mikkelsen, An implicit method for modeling the simultaneous transport and metabolism of pilocarpine prodrugs across the excised rabbit cornea, Lilly Modeling Conference, (1987).

GL Mosher, H Bundgaard, E Falch and C Larsen, Effects of drug-protein binding on the precorneal loss of pilocarpine prodrugs, 1st Annual AAPS National Meeting, (1986).

GL Mosher, T Mikkelsen, H Bundgaard, E Falch and C Larsen, Prodrug-to-drug ocular bioconversion of pilocarpic acid diesters, 39th Annual APS Meeting, (1985).

GL Mosher, T Mikkelsen, H Bundgaard, E Falch and C Larsen, Pilocarpine prodrugs. II. Comparative miotic activities of pilocarpic acid esters in the rabbit following topical instillation, 37th Annual APS Meeting, (1984).

H Bundgaard, E Falch, C Larsen, GL Mosher and T Mikkelsen, S Pilocarpine prodrugs. I. Synthesis, physicochemical properties and kinetics of lactonization of pilocarpic acid esters, 37th Annual APS Meeting, (1984).

GL Mosher, Pharmacokinetics - principles and application, Pharmacy Continuing Education Fall Seminar Circuit, University of Kansas, (1984).

GL Mosher, T Mikkelsen and K Himmelstein, Diffusion of a series of homogenous compounds across single and laminated polymeric membranes. 15th Annual Graduate Student Pharmaceutical Research Meeting, (1983).

GL Mosher and T Mikkelsen, Corneal uptake of the n-alkyl p-aminobenzoate homologs, 27th Annual APS National Meeting, (1979)

GL Mosher and T Mikkelsen, Transport across the isolated corneal membrane and physicochemical drug properties, 125th Annual APhA National Meeting, Montreal, Canada (1978).

Attorney Docket No. 43060-707.305
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	MOSHER; Gerold L. et al.	Group Art Unit:	1629
Serial Number:	16/242,898	Examiner:	SPRINGER; Stephanie K.
Filing or 371 (c) Date:	2019-01-08	CONFIRMATION NO:	1032
Title:	ENALAPRIL FORMULATIONS		

FILED ELECTRONICALLY ON: August 23, 2019

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☐ *37 CFR § 1.97 (b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
-- OR --
 - ☐ (3) It is being filed before the mailing of a first Office action on the merits;
-- OR --
 - ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☒ *37 CFR § 1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97 (e) provided concurrently herewith;
-- OR --
 - ☒ a fee of \$240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR § 1.97 (d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
-- AND --
 - ii. a fee of \$240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☐ *37 CFR §1.97 (e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
-- AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☐ *Statement Under 37 C.F.R. §1.704(d)*. Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☒ *37 CFR §1.98 (a) (2)*. The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☐ *37 CFR §1.98(a)(3)*. The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
- OR --
- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☐ *37 CFR §1.98(d)*. Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$240.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.43060-707.305).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: September 3, 2019

By: /Clark Lin/

Clark Y. Lin, Ph.D., Esq.
Registration No. 67,024

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/242,898	01/08/2019	Gerold L. MOSHER	43060-707.305	1032
21971 7590 11/19/2019 WILSON, SONSINI, GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 94304-1050			<div>EXAMINER</div> <div>SPRINGER, STEPHANIE K</div>	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			11/19/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):
patentdocket@wsgr.com

Office Action Summary**Application No.**

16/242,898

Applicant(s)

MOSHER et al.

Examiner

STEPHANIE K SPRINGER

Art Unit

1629

AIA (FITF) Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 1 August 2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a) ☒ This action is **FINAL**.

2b) ☐ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-7,9-22 and 24-30 is/are pending in the application.

5a) Of the above claim(s) ____ is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1-7,9-22 and 24-30 is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date ____.

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: ____.

Paper No(s)/Mail Date 2 pgs, 9/3/19.

Application/Control Number: 16/242,898
Art Unit: 1629

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DETAILED ACTION

Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

This application is a continuation of application 16/177,159, filed on October 31, 2018, which is a continuation of application 16/003,994, now US Patent 10,154,987, filed on June 8, 2018, which is a continuation of application 15/802,341, now US Patent 10,039,745, filed on November 2, 2017, which is a continuation of application 15/613,622, now US Patent 9,808,442, filed on June 5, 2017, which is a continuation of application 15/081,603, now US Patent 9,669,008, filed on March 25, 2016 and claims priority to US provisional application 62/310,198, filed on March 18, 2016.

This application was granted Track One status on February 14, 2019.

Applicant's amendments filed August 1, 2019 canceling claims 8 and 23 are acknowledged.

Applicant's arguments, filed August 1, 2019, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn.

Claims 1-7, 9-22, and 24-30 are examined on the merits herein as they read upon the elected species.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on September 3, 2019 has been considered by the examiner. The submissions are in compliance with the provisions of 37 CFR §§ 1.97 and 1.98. Enclosed with this Office Action is a return-copy of the Forms PTO-1449 with the examiner's initials and signature indicating those references that have been considered.

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Terminal Disclaimer

The terminal disclaimer filed on August 1, 2019 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patents 9,669,008; 9,808,442; 10,039,745; and 10,154,987, and copending application 16/177,159, has been reviewed and is accepted. The terminal disclaimer has been recorded.

Response to Arguments

Declaration under 37 CFR 1.132

The Declaration under 35 CFR 1.132 submitted on August 1, 2019 has been considered by the Examiner. The declaration under 37 CFR 1.132 is insufficient to overcome the rejections of claims 1-7, 9-22, and 24-30, as it fails to provide data corroborating the Applicant's allegations that the claimed compositions provide unexpected results over the compositions disclosed in the prior art.

The Declaration, dated February 2, 2017, is directed towards application 15/081,603, now US Patent 9,669,008. The Declaration alleges that the enalapril oral liquid formulations of '603 "provides several advantages", particularly improved ease of administration; patient compliance; and accuracy of dosing. The Declaration contends that the enalapril oral liquid formulations "of the present claims", that is, the claims of '603, are stable at 5 ± 3 °C for 12 months or longer with minimal degradation.

The Declaration presents exemplary formulations E7 and E8:

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Composition of Enalapril Maleate Formulations		
Component	E7	E8
Enalapril maleate	1.00	1.00
Citric acid anhydrous	1.80	1.82
Sodium citrate anhydrous	0.16	0.15
Sodium benzoate	1.00	1.00
Sucralose	0.70	0.70
Mixed berry flavor	0.50	0.50
Water	qs	qs
pH (measured)	3.3	3.3
qs = sufficient quantity		

It appears that these refer to percentages of the total composition. Thus, formulations E7 and E8 are directed to aqueous compositions comprising

- a) enalapril maleate in an amount of 1.00%;
- b) citric acid and sodium citrate in a total amount of 1.96% or 1.97%;
- c) sodium benzoate in an amount of 1.00%;
- d) sucralose in an amount of 0.70%;
- e) flavoring in an amount of 0.50%.

The Applicant's attention is directed towards MPEP § 716.02, Allegations of Unexpected Results: "Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected."

In order to demonstrate unexpected results, a comparison between the claimed invention and the closest prior art must be evaluated. By way of comparative examples, the Applicant offers compositions representing Nahata, prepared using a) water, b), either citrate buffer at a pH of 5.0, or c) a 1:1 mixture of Ora-Plus and Ora-Sweet (Tables A and B, Figures 1 and 2).

While Applicant has provided evidence demonstrating the unexpected stability of formulations E7 and E8 as compared to the compositions of Nahata, the formulations E7 and E8

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are essentially identical, and limited to a single embodiment of the claimed invention. The Examiner notes that the instantly claimed invention is drawn to aqueous compositions comprising

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer to maintain the pH about 4.5 or below; and

(iii) about 1 mg/mL of a preservative that is sodium benzoate.

The inventive compositions of E7 and E8 are limited to compositions comprising

a) enalapril maleate in an amount of 1.00%;

b) citric acid and sodium citrate in a total amount of 1.96% or 1.97%;

c) sodium benzoate in an amount of 1.00%.

The disclosure of a single buffer combination in a single amount fails to adequately address the scope of “a buffer to maintain the pH about 4.5 or below”. Thus, Applicant has failed to provide data supporting the breadth of the claims. MPEP § 716.02(d) addresses the subject of unexpected results commensurate in scope with the claimed invention: “Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the “objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.” In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. See *In re Peterson*, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir.1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims.). However, the subject matter

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circumscribed by the instant claims extends well beyond the metes and bounds of these discrete embodiments potentially demonstrated to exert unexpected results over the prior art compositions, as the Applicant has proffered a single aqueous composition comprising a) enalapril maleate in an amount of 1.00%; b) citric acid and sodium citrate in a total amount of 1.96% or 1.97%; and c) sodium benzoate in an amount of 1.00%. As the instant claims are drawn to compositions comprising (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer to maintain the pH about 4.5 or below; and (iii) about 1 mg/mL of sodium benzoate, the claims are not commensurate in scope with the disclosed embodiments. Applicant has failed to address why the data from the exemplified combinations are indicative of unexpected results over the entire scope of subject matter instantly claimed.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 1-7, 9-22, and 24-30 under 35 U.S.C. 103 as obvious over Nahata et al., "Stability of enalapril maleate in three extemporaneously prepared oral liquids", *Am. J. Health-Syst. Pharm.*, 1998, vol. 55, pages 1155-1157 (cited in IDS) in view of Sosnowska et al., "Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared From Commercially Available Tablets", *Acta Poloniae Pharmaceutica – Drug Research*, 2009, vol. 66, no. 3, pages 321-326 (cited in PTO-892) in view of Boukarim et al., "Preservatives in Liquid Pharmaceutical Preparations", *J. Appl. Res.*, 2009, vol. 9, no. 1&2, pages 14-17 (cited in PTO-

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892), is **maintained** for the reasons set forth at pages 5-10 of the Office Action dated May 2, 2019, of which said reasons are herein incorporated by reference.

Reiterated Rejection

Claims 1-7, 9-22, and 24-30 are rejected under 35 U.S.C. 103 as obvious over Nahata et al., "Stability of elanapril maleate in three extemporaneously prepared oral liquids", *Am. J. Health-Syst. Pharm.*, 1998, vol. 55, pages 1155-1157 (cited in IDS) in view of Sosnowska et al., "Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared From Commercially Available Tablets", *Acta Poloniae Pharmaceutica – Drug Research*, 2009, vol. 66, no. 3, pages 321-326 (cited in PTO-892) in view of Boukarim et al., "Preservatives in Liquid Pharmaceutical Preparations", *J. Appl. Res.*, 2009, vol. 9, no. 1&2, pages 14-17 (cited in PTO-892).

Claims 1-7, 9-22, and 24-30 are generally drawn to compositions comprising:

- (i) about 0.6 to about 1.2 mg/ml, or about 10% to about 25% (w/w/ of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer to maintain the pH about 4.5 or below;
- (iii) about 1 mg/ml or 19% (w/w of solids) of a preservative that is sodium benzoate; and
- (iv) water.

Nahata teaches formulations comprising

- (i) 1 mg/ml enalapril;
- (ii) a buffer comprising citric acid and sodium citrate;
- (iii) a preservative; and
- (iv) water.

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In particular, Nahata teaches preparation of an aqueous solution comprising 1 mg/ml enalapril in a citrate buffer solution (page 1156, column 1, paragraph 2). The citrate buffer solution is prepared accordingly: "Prepare the isotonic citrate buffer solution (pH 5.0) by dissolving 0.353 g of Citric Acid Monohydrate Granular, USP, 1.01 g of Sodium Citrate Dihydrate Granular, USP, and 0.54 g of sodium chloride in 100 mL of distilled water" (page 1157, Appendix and footnote a). The ordinarily skilled artisan would recognize the sodium chloride in the citrate buffer solution taught by Nahata to meet the instant requirements of a preservative; see Parish, "How do salt and sugar prevent microbial spoilage?", *Scientific American*, 2006 (cited in PTO-892; cited to show a fact).

Nahata also teaches an aqueous solution comprising 1 mg/ml enalapril in a mixture of Ora-Sweet and Ora-Plus (page 1156, column 1, paragraph 2). Ora-Sweet and Ora-Plus are commercially available from Paddock Laboratories (page 1157, footnotes d and e). Ora-Sweet is an aqueous solution comprising sucrose, glycerin, sorbitol, flavoring, citric acid, sodium phosphate, methylparaben, and potassium sorbate; Ora-Plus is an aqueous solution comprising microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, flavoring, citric acid, sodium phosphate, simethicone, methylparaben, and potassium sorbate; both Ora-Sweet and Ora-Plus have a pH of 4.2. Thus, the formulation taught by Nahata comprising 1 mg/ml enalapril in a mixture of Ora-Sweet and Ora-Plus comprises

- (i) 1 mg/ml enalapril;
- (ii) citric acid;
- (iii) a preservative, such as methylparaben; and
- (iv) water.

The formulations comprising Ora-Sweet and Ora-Plus also comprise sweeteners and flavoring agents, while not containing mannitol or silicon dioxide, thereby meeting the requirements of claims 2, 4-7, 16-22, 29, and 30.

Thus, Nahata teaches aqueous compositions comprising

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- (i) 1 mg/ml enalapril;
- (ii) citric acid and sodium citrate;
- (iii) a preservative, such as methylparaben; and
- (iv) water.

Similarly, Sosnowska teaches formulations comprising

- (i) 1 mg/ml enalapril;
- (ii) citric acid and citrate buffer;
- (iii) 0.2% methylhydroxybenzoate as a preservative, *i.e.*, methylparaben; and
- (iv) water.

Sosnowska teaches liquid formulations of enalapril, prepared from crushed enalapril tablets. Sosnowska generally teaches compositions comprising enalapril maleate in deionized water, citrate buffer solution, carboxymethylcellulose as a suspending agent, and methyl hydroxybenzoate 0.2% as a preservative. Sosnowska teaches that the maximum stability of enalapril maleate is at a pH of about 3; “therefore the pH value of prepared formulations was adjusted to 3.0 using citric acid” (page 322, column 1, “Formulations preparation”). Regarding stability, Sosnowska notes:

“The tablet suspension in water would be expected to readily support microbial growth, especially at room temperature during in-use conditions, therefore 0.2% methyl hydroxybenzoate as compatible with the drugs preservative was added (17). No colonies or other evidence of bacterial or fungal growth were detected for any of the formulations tested. There was also no detectable change in color, odor, and taste in any sample. However, in the absence of microbiological data, the shelf-life given to extemporaneous products containing preservatives is usually 30 days - the time period in which the formulations were tested.” (page 325, column 2, paragraph 3).

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Thus Nahata and Sosnowska teach liquid compositions comprising 1 mg/ml enalapril, a citrate buffer, 0.2% w/w preservative, and water. Although both Nahata and Sosnowska teach the use of a preservative, Nahata and Sosnowska do not teach the use of sodium benzoate as a preservative.

Boukarim is directed towards preservatives in liquid pharmaceutical formulations. Boukarim teaches that sodium benzoate, potassium sorbate, and methyl hydroxybenzoate are commonly used as preservatives in liquid pharmaceutical preparations. Boukarim states, "Among the most commonly used preservatives in the conservation of liquid pharmaceutical preparations are sodium benzoate, potassium sorbate, and methyl hydroxybenzoate (methyl-paraben). Their typical allowed concentrations range respectively from 0.1-0.2%, 0.1-0.2%, and 0.1-0.25% (w/w) (page 14, column 2). Boukarim notes that sodium benzoate is ineffective when formulated at a pH > 5 (page 16, column 2).

The ordinarily skilled artisan would have had a reasonable expectation of success in arriving at the instantly claimed composition in view of the combined teachings of Nahata, Sosnowska, and Boukarim. Nahata and Sosnowska are directed towards liquid formulations of enalapril; both Nahata and Sosnowska teach compositions comprising a) 1 mg/ml enalapril, b) citric acid and/or citrate buffer, c) a preservative, and d) water. Although Nahata and Sosnowska teach methylparaben as a preferred preservative, the ordinarily skilled artisan would recognize methylparaben and sodium benzoate to be functional equivalents in view of the teachings of Boukarim. Boukarim teaches that methylparaben and sodium benzoate are two of the three most common preservatives used for liquid pharmaceutical formulations. As both methylparaben and sodium benzoate are commonly used preservatives known to be suitable for use in liquid formulations, it would be within the purview of the ordinarily skilled artisan to arrive at the instantly claimed formulation in view of Boukarim, Nahata, and Sosnowska. In other words, one would find it *prima facie* obvious to substitute the sodium benzoate preservative taught by Boukarim for the methylparaben preservative taught by Nahata and Sosnowska. The Examiner notes that

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Boukarim particularly teaches the use of sodium benzoate in an amount meeting the instant requirements, and Boukarim explicitly teaches that sodium benzoate is ineffective at a pH > 5. Accordingly, one would find sodium benzoate to be suitable for use in a liquid formulation comprising enalapril, which is ideally at a pH of 3.0. Absent evidence of criticality in the selection of a particular preservative, a particular buffer, or particular amounts of each of the components, optimizing the formulations taught by Nahata and Sosnowska would fall within routine optimization for the ordinarily skilled artisan.

Regarding the limitations directed towards the pH of the formulation, Nahata teaches a citrate buffer having a pH of 5, and an Ora-Sweet/Ora-Plus mixture having a pH of 4.2. Sosnowska also teaches the optimal pH of an enalapril formulation, namely, a pH of 3.0. Thus, Nahata and Sosnowska meet the instant limitations of a formulation having a pH of “about 3 and about 3.5” and “about 3.3” as recited in claims 10, 11, 25, and 26. The use of the word “about” in a claim is appropriate where the claim contains a range of components with no absolute boundaries, and is only limited to the extent that prior art exists which would limit broad interpretation of the claim. See *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1217-1218, 18 USPQ2d 1016 (Fed. Cir. 1991).

Although Nahata and Sosnowska do not explicitly teach that the formulation is stable at about 5 ± 3 °C for at least 12 months, or that the formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period, the combined teachings of Nahata, Sosnowska, and Boukarim meet the instantly claimed requirements, and absent evidence to the contrary, one would expect the composition to have the same properties as instantly claimed. Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily

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present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Response to Arguments

Applicant's arguments filed August 1, 2019 have been fully considered but they are not persuasive.

Applicant generally contends that the cited references do not teach or suggest enalapril oral liquid formulations which are stable at about 5 ± 3 °C for at least 12 months. Applicant further alleges that the extemporaneously prepared formulations of Nahata and Sosnowska would not have the claimed stability, and there would be no reasonable expectation of the claimed stability in said extemporaneously prepared formulations. Applicant alleges that the claimed invention results in compositions exhibiting improved stability.

Applicant's remarks regarding the teachings of Nahata, Sosnowska, and Boukarim are not found persuasive. Applicant contends that the extemporaneously prepared formulation of Nahata contains 19 components in addition to enalapril and water, and there is no guidance or teaching to suggest which of these components is necessary for stability, or which components could be varied or eliminated. As a first matter, the Examiner notes that the instantly claimed invention is drawn to a formulation ***comprising***

- (i) about 0.6 to about 1.2 mg/ml, or about 10% to about 25% (w/w/ of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;
- (ii) a buffer to maintain the pH about 4.5 or below;
- (iii) about 1 mg/ml or 19% (w/w of solids) of a preservative that is sodium benzoate; and
- (iv) water.

While the compositions exemplified by Nahata comprise additional components, there is no explicit proviso which would exclude the use of additional components in the instantly claimed

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formulation. Applicant's attention is directed towards MPEP § 2111.03: The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Mars Inc.v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837,1843 (Fed. Cir. 2004) ("like the term 'comprising,' the terms 'containing' and 'mixture' are open-ended."); *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364,1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948)("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). In *Gillette Co. v. Energizer Holdings Inc.*, 405 F.3d 1367,1371-73, 74 USPQ2d 1586, 1589-91 (Fed. Cir. 2005), the court held that a claim to "a safety razor blade unit comprising a guard, a cap, and a group of first, second, and third blades" encompasses razors with more than three blades because the transitional phrase "comprising" in the preamble and the phrase "group of" are presumptively open-ended. "The word 'comprising' transitioning from the preamble to the body signals that the entire claim is presumptively open-ended." *Id.* In contrast, the court noted the phrase "group consisting of" is a closed term, which is often used in claim drafting to signal a "Markush group" that is by its nature closed. *Id.* The court also emphasized that reference to "first," "second," and "third" blades in the claim was not used to show a serial or numerical limitation but instead was used to distinguish or identify the various members of the group. *Id.* In the instant case, the claimed composition may further comprise unrecited components, including any of the other components taught by Nahata.

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Nahata and Sosnowska are directed towards liquid formulations of enalapril; both Nahata and Sosnowska teach compositions comprising a) 1 mg/ml enalapril, b) citric acid and/or citrate buffer, c) a preservative, and d) water. The combined teachings of Nahata and Sosnowska render the instantly claimed invention *prima facie* obvious to one having ordinary skill in the art. While the Examiner acknowledges that both Nahata and Sosnowska are directed towards formulations created by crushing enalapril tablets and adding water, thereby converting the oral solid formulation to an oral liquid formulation, the Examiner notes that one having ordinary skill in the art would reasonably recognize which components could be removed from the extemporaneously prepared formulation, in view of the level of skill of a formulations scientist. One would reasonably recognize that certain components in the oral solid formulations used by Nahata and Sosnowska are components used to achieve a solid formulation; one would recognize that these components would not be necessary in a liquid formulation. The fact that Applicant monitored and observed the stability of the composition does not imbue an inventive concept to the composition which was obvious in view of the combined teachings of Nahata and Sosnowska. Absent evidence of unexpected results or criticality in the selection of a particular component or the amount of the component, the instantly claimed composition would have been obvious to the ordinarily skilled artisan, in view of the combined teachings of Nahata and Sosnowska, in view of the level of skill of one having ordinary skill in the art.

Regarding the alleged unexpected results, Applicant's remarks regarding the alleged unexpected results presented in the Declaration filed August 1, 2019 have been addressed *supra*. As noted therein, the instant claims are drawn to compositions comprising (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer to maintain the pH about 4.5 or below; and (iii) about 1 mg/mL of sodium benzoate, and thus, the claims are not commensurate in scope with the disclosed embodiments.

Thus the rejection is proper, and is maintained.

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Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JEFFREY S LUNDGREN whose telephone number is (571)272-5541. The examiner can normally be reached on Monday through Thursday from 8 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren, can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-270-8380.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stephanie Springer/
Examiner, Art Unit 1629

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/JEFFREY S LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL (Submitted Only via EFS-Web)							
Application Number	16/242,898	Filing Date	2019-01-08	Docket Number (if applicable)	43060-707.305	Art Unit	1629
First Named Inventor	Gerold L. Mosher et al.			Examiner Name	Stephanie K. Springer		
This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application. Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV							
SUBMISSION REQUIRED UNDER 37 CFR 1.114							
Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).							
<input type="checkbox"/> Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.							
<input type="checkbox"/> Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____							
<input type="checkbox"/> Other _____							
<input checked="" type="checkbox"/> Enclosed							
<input checked="" type="checkbox"/> Amendment/Reply							
<input type="checkbox"/> Information Disclosure Statement (IDS)							
<input checked="" type="checkbox"/> Affidavit(s)/ Declaration(s)							
<input type="checkbox"/> Other _____							
MISCELLANEOUS							
<input type="checkbox"/> Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)							
<input type="checkbox"/> Other _____							
FEES							
<input checked="" type="checkbox"/> The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed. The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No <u>232415</u>							
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED							
<input checked="" type="checkbox"/> Patent Practitioner Signature Applicant Signature							

Signature of Registered U.S. Patent Practitioner			
Signature	Clark Lin/	Date (YYYY-MM-DD)	2020-05-14
Name	Clark Y. Lin	Registration Number	67024

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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Attorney Docket No. 43060-707.305

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 1032
Serial No.: 16/242,898	Examiner: SPRINGER, Stephanie K
Filed: January 8, 2019	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on May 14, 2020, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u>/Paula Derby/</u></p>

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132

I, **Gerold Mosher**, state and declare as follows:

1. I am currently employed at Azurity Pharmaceuticals, Inc., a company formed in May 2019 by the acquisition of Silvergate Pharmaceuticals, Inc. by CutisPharma, Inc.
2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.
3. I have been employed at Silvergate Pharmaceuticals and now Azurity Pharmaceuticals since 2013, and my current position is Vice President of Product Development. As part of my job duties, I develop oral formulations for pediatric use. I have a small laboratory where I

develop, characterize and move formulations through the steps required for FDA approval and eventual sale.

4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also been employed by small startup companies to develop new solubilizing technology for oral, injectable, and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for about 40 years, and have extensive experience in developing pharmaceutical formulations. My *Curriculum Vitae* is attached as Exhibit A.

6. I am familiar with the subject matter claimed in U.S. Pat. App. Ser. No. 16/242,898 (“the ’898 application”), and I am a named inventor on this application. Silvergate Pharmaceuticals, Inc. is the assignee of all rights in the invention of the pending ’898 application.

7. I am aware of the Final Office Action mailed in this matter on November 19, 2019. I am also aware that the pending claims stand rejected as allegedly being obvious under 35 U.S.C. 103 over Nahata et al., “Stability of enalapril maleate in three extemporaneously prepared oral liquids,” Am. J. Health-Syst. Pharm., 1998, vol. 55, pages 1155-1157 (“Nahata”) in view of Sosnowska et al., “Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared From Commercially Available Tablets,” Acta Poloniae Pharmaceutica - Drug Research, 2009, vol. 66, no. 3, pages 321-326 (“Sosnowska”) in view of Boukarim et al., “Preservatives in Liquid Pharmaceutical Preparations”, J. Appl. Res., 2009, vol. 9, no. 1&2, pages 14-17 (“Boukarim”). I have reviewed these cited references in the Final Office Action.

8. I am submitting this declaration to address the comments made in the Office Action.

9. The ’898 application relates to enalapril oral liquid formulations that are stable at about 5 ± 3 °C for at least 12 months. The development of this described enalapril formulation was oriented on preparing a safe, stable, uniform oral liquid with minimal degradation and having an acceptable taste for pediatric patients.

10. Traditionally, approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in “Nahata” and subsequently administering the suspension to the patient, or (3) reconstituting a powder in a liquid carrier. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty swallowing solid oral dosage forms. For the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination.

11. As compared to these currently available methods, the enalapril oral liquid formulation claimed in the '898 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

12. The oral enalapril liquid formulations of the '898 application have superior stability—they are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

13. Evidence of the superior stability of the formulations disclosed in the '898 application can be found in exemplary formulations H1 to H9. Formulations H1 to H9 were prepared according to the compositions in Table 1 and titrated if needed to the target pH with 5N hydrochloric acid or 5N sodium hydroxide. The formulations were placed into HDPE containers and sealed with screw caps and induction sealing. The formulations were stored at 5 °C and 25 °C and sampled at various times. Samples were analyzed by HPLC for enalapril maleate and enalapril related substances. The results of the analyses are presented in Table 2.

14. As shown in Table 1 below, formulations H1- H9 were prepared with a variety of buffers, including sodium citrate, citric acid, phosphate, citrate/phosphate, acetate, glycine, and tartrate. Formulations H1 and H7-H9 contain citrate-based buffers. Specifically, formulation H1 was prepared with citric acid and sodium citrate, and formulations H7-H9 were prepared with citric acid only (no sodium citrate) with the pH being adjusted with HCl or NaOH. Formulations H2-H6 were prepared with phosphate, citrate/phosphate, acetate, glycine, and tartrate buffer, respectively. The pH values of formulations H1 to H9 vary from about 3.3 to about 4.5. The initial pH values of formulations H1 to H7 are about 3.3, and the initial pH values of formulations H8 and H9 are about 4.0 and 4.5, respectively.

15. The enalapril maleate assay results in Table 2 show that all the formulations have greater than 98% of the initial enalapril maleate content remaining after 52 weeks at 5 °C. The total impurity content is also less than 2% for the same period showing comparable stability between the formulations, irrespective of the type of buffers used.

Table 1

Ingredients	Compositions (mg/mL) for Stability Testing at 5 °C and 25 °C								
	H1	H2	H3	H4	H5	H6	H7	H8	H9
	Citrate	Phosphate	Citrate/ Phosphate	Acetate	Glycine	Tartrate	Citrate	Citrate	Citrate
Acetic acid, glacial	-	-	-	0.58	-	-	-	-	-
Sodium Acetate	-	-	-	0.04	-	-	-	-	-
Citric acid, anhydrous	1.82	-	1.07	-	-	-	1.92	1.92	1.92
Sodium citrate, dihydrate	0.15	-	-	-	-	-	-	-	-
Glycine	-	-	-	-	0.75	-	-	-	-
Sodium dihydrogen phosphate, anhydrous	-	1.2	-	-	-	-	-	-	-
Disodium hydrogen	-	-	0.63	-	-	-	-	-	-

phosphate, anhydrous

L-(+)-tartaric acid	-	-	-	-	-	0.75	-	-	-
Sodium tartrate dibasic, dihydrate	-	-	-	-	-	1.15	-	-	-
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose NF	0.70	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
pH	3.3	3.3	3.3	3.3	3.3	3.3	3.3	4.0	4.5

Table 2

Assay and Total Degradant Content After Storage											
	Storage		Formulation								
	°C	Weeks	H1	H2	H3	H4	H5	H6	H7	H8	H9
Enalapril Maleate (% initial)	5	0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
		2	100.1	100.1	99.7	100.0	99.5	98.2	100.7	100.4	100.3
		4	100.2	100.3	99.6	100.4	100.0	98.9	99.8	100.0	99.6
		8	100.0	100.0	99.7	100.0	99.5	98.5	99.6	100.9	100.7
		24	99.8	100.0	99.6	100.2	99.4	98.6	100.4	100.1	99.8
		28	99.8	99.9	99.6	100.1	99.3	98.4	99.7	-	-
		36	-	-	-	-	-	-	-	99.9	99.4
		52	99.9	99.9	99.7	99.7	98.9	98.1	99.8	99.5	99.2
	25	0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
		2	100.1	99.2	99.7	100.0	99.5	98.4	99.8	99.9	99.5
		4	99.7	99.1	99.4	99.9	99.4	98.5	99.1	99.0	98.1
		8	98.8	98.0	98.5	99.0	98.3	97.4	98.3	99.3	97.7
		24	98.0	97.2	97.7	98.4	98.1	96.9	98.4	97.5	95.3
		28	95.8	95.1	95.5	96.5	96.1	94.7	95.6	-	-
		36	-	-	-	-	-	-	-	93.7	89.4
		52	93.9	93.3	93.5	94.3	93.9	92.4	93.6	91.7	86.0
Total Impurities (% w/w of enalapril maleate)	5	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.09	0.10
		2	0.07	0.07	0.07	0.06	0.06	0.06	0.07	0.14	0.16
		4	0.09	0.11	0.10	0.11	0.11	0.12	0.10	0.20	0.26
		8	0.18	0.20	0.18	0.16	0.16	0.18	0.18	0.31	0.41
		24	0.25	0.29	0.26	0.24	0.22	0.25	0.27	0.43	0.60
		28	0.44	0.47	0.47	0.42	0.41	0.44	0.46	-	-
		36	-	-	-	-	-	-	-	0.91	1.20
		52	0.68	0.71	0.71	0.64	0.66	0.68	0.65	1.18	1.53
	25	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.09	0.10
		2	0.46	0.47	0.47	0.39	0.39	0.41	0.51	0.63	0.95
		4	0.86	0.91	0.89	0.83	0.81	0.88	0.89	1.16	1.84
		8	1.71	1.79	1.76	1.53	1.51	1.64	1.70	2.21	3.49
		24	2.52	2.65	2.60	2.24	2.21	2.40	2.49	3.28	5.27
		28	4.91	5.18	5.08	4.49	4.43	4.81	4.94	-	-

36	-	-	-	-	-	-	-	7.32	11.60
52	7.22	7.64	7.45	6.67	6.60	7.16	7.25	9.55	14.95

16. Further evidence of the superior stability of the formulations disclosed in the '898 application can be found in exemplary formulations in Table 3. Formulations in Table 3 were prepared using fumarate, tartrate, malate, aspartate, glycinate, lactate, formate, phthalate, acetate, succinate, gluconate, glutamate, citrate, phosphate, and citrate/phosphate buffers, respectively. Specifically, these formulations were prepared according to the compositions in Table 3 and titrated if needed to pH 3 and 4 with 5N hydrochloric acid or 5N sodium hydroxide. The formulations were placed into amber glass screw-capped vial with Teflon lined caps. The vials were capped, stored at 60 °C and sampled at various times over 7 days. Samples were analyzed by HPLC for enalapril. The results of the analyses are presented in Table 4.

17. The citrate and phosphate 10mM formulations were included in Table 3 as a control since citrate and phosphate buffers were included in the previous study in Tables 1 and 2 and demonstrated superior stability. The enalapril maleate assay results in Table 4 show that all the formulations have stability comparable to the citrate formulations at 60 °C.

Table 3

Compositions (mg/mL) for Stability Testing at 60 °C												
Formula	Fumarate		Tartrate		Malate		Aspartate		Glycinate		Lactate	
	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM
Fumaric acid	2.32	1.16	-	-	-	-	-	-	-	-	-	-
Tartaric acid	-	-	3.00	1.50	-	-	-	-	-	-	-	-
DL-Malic acid	-	-	-	-	2.68	1.34	-	-	-	-	-	-
L-Aspartic acid	-	-	-	-	-	-	2.66	1.33	-	-	-	-
Glycine	-	-	-	-	-	-	-	-	1.50	0.75	-	-
Lactic acid	-	-	-	-	-	-	-	-	-	-	180	90
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
5N HCl/5N NaOH to pH	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0
Formula	Formate		Phthalate		Acetate		Succinate		Gluconate		Glutamate	
	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM
Formic acid	0.92	0.46	-	-	-	-	-	-	-	-	-	-

Potassium hydrogen phthalate	-	-	4.08	2.04	-	-	-	-	-	-	-	-
Acetic acid, glacial	-	-	-	-	1.20	0.60	-	-	-	-	-	-
Succinic acid	-	-	-	-	-	-	2.36	1.18	-	-	-	-
Sodium gluconate	-	-	-	-	-	-	-	-	4.36	2.18	-	-
L-Glutamic acid	-	-	-	-	-	-	-	-	-	-	2.94	1.47
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
5N HCl/5N NaOH to pH	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0

Formula	Citrate		Phosphate		Citrate/Phosphate	
	20mM	10mM	20mM	10mM	10mM each	
Citric acid, anhydrous	3.84	1.92	-	-	1.92	
Phosphoric acid	-	-	196	98	98	
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	
Purified water	Qs	Qs	Qs	Qs	Qs	
5N HCl/5N NaOH to pH	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	

TABLE 4

Assay Results After Storage of Formulations at 60 °C

Buffer	mM	Enalapril Maleate, pH 3 (% initial)				Enalapril Maleate, pH 4 (% initial)			
		0 Days	2 Days	4 Days	7 Days	0 Days	2 Days	4 Days	7 Days
Citrate	10	100.0	97.1	97.2	95.5	100.0	97.2	96.6	94.6
	20	100.0	97.1	96.8	95.2	100.0	96.8	96.4	94.4
Phosphate	10	100.0	97.1	97.1	95.3	100.0	96.3	96.2	94.5
	20	100.0	97.1	96.7	95.2	100.0	96.3	96.0	94.2
Citrate/Phosphate	20	100.0	96.8	97.3	95.2	100.0	96.8	96.2	94.9
Tartrate	10	100.0	97.4	97.6	95.9	100.0	96.9	97.0	95.2
	20	100.0	97.2	97.6	95.6	100.0	97.1	96.4	94.0
Glycinate	10	100.0	98.7	96.4	95.4	100.0	96.8	96.6	95.3
	20	100.0	98.3	96.9	95.7	100.0	96.7	97.3	96.0
Acetate	10	100.0	97.5	97.4	95.1	100.0	96.7	96.8	95.3
	20	100.0	97.4	98.2	95.2	100.0	97.1	96.8	94.9
Malate	10	100.0	97.2	97.1	96.0	100.0	97.0	96.8	95.2
	20	100.0	97.2	97.1	95.9	100.0	96.7	96.5	95.0
Fumarate	10	100.0	96.6	96.8	95.2	100.0	95.9	96.1	94.4
	20	100.0	96.6	96.6	94.7	100.0	95.8	95.8	93.6
Succinate	10	100.0	98.1	96.2	95.3	100.0	96.6	96.8	94.5

	20	100.0	96.9	97.3	95.1	100.0	96.2	96.9	94.6
Aspartate	10	100.0	97.3	97.1	96.1	100.0	96.5	98.1	96.4
	20	100.0	97.0	97.4	95.8	100.0	96.6	97.0	95.3
Formate	10	100.0	97.0	97.1	95.6	100.0	96.6	97.1	93.8
	20	100.0	96.9	96.5	96.3	100.0	96.1	98.1	93.3
Gluconate	10	100.0	97.2	97.9	95.2	100.0	96.3	96.2	93.4
	20	100.0	97.0	98.9	94.2	100.0	96.2	95.8	94.2
Glutamate	10	100.0	97.2	96.9	95.9	100.0	96.9	96.4	95.3
	20	100.0	97.3	97.1	95.2	100.0	96.7	97.5	93.7
Lactate	10	100.0	97.3	97.1	96.4	100.0	96.5	98.3	95.3
	20	100.0	97.3	97.2	97.2	100.0	96.9	96.3	95.2
Phthalate	10	100.0	97.3	96.9	95.8	100.0	96.2	96.2	94.7
	20	100.0	97.0	96.8	95.5	100.0	96.2	97.8	93.3

18. As presented above, Tables 1-4 show that the formulations of the '898 application can be prepared using a variety of buffers (e.g., citrate, phosphate, citrate/phosphate, acetate, glycinate, fumarate, tartrate, malate, aspartate, lactate, formate, phthalate, acetate, succinate, gluconate, and glutamate buffers) and the pH values of the formulations can vary, e.g., at least from about 3 to about 4.5. All the formulations in Tables 1 and 3 demonstrated superior stability—retaining greater than 98% of the initial enalapril maleate content and having less than 2% w/w total impurity after 52 weeks at 5 °C, or having comparable stability when tested under an accelerated condition of 60 °C.

19. In my review of the references cited in the Office Action, none of the references describe this stability of at least 12 months at 5±3 °C or any means of achieving this stability for enalapril formulations.

20. I have reviewed Nahata which describes the extemporaneous preparation of oral liquid enalapril formulations by crushing enalapril tablets with a mortar and pestle and suspending the resulting ground tablets in water, citrate buffer, or Ora-Plus/Ora-Sweet. On stability, Nahata states that the “compounded oral liquids [were] stable for 91 days at 4 and 25 °C” defining stable as “concentration after storage was ≥90% of the initial concentration. Table 1 of Nahata shows that the enalapril extemporaneous formulations exhibited about 5% loss of enalapril after about 56 days at 4 °C and about 5% loss of enalapril after about 91 days at 25 °C.

21. I have reviewed Sosnowska, which similarly describes extemporaneous enalapril suspensions. The suspensions disclosed in Sosnowska were obtained by grinding tablets and suspending the resultant powder in a hydroxyethylcellulose solution or in a mixture that contains raspberry syrup and hydroxyethylcellulose solution. Based on the 30-day stability data shown in Table 1 of Sosnowska, these extemporaneous formulations have comparable stabilities to the formulations of Nahata, which is retaining about 98% of initial enalapril concentration after stored at refrigerated condition for 30 days. As noted in Sosnowska, “in the absence of microbiological data, the shelf-life given to extemporaneous products containing preservatives is usually 30 days.” Page 325 of Sosnowska.

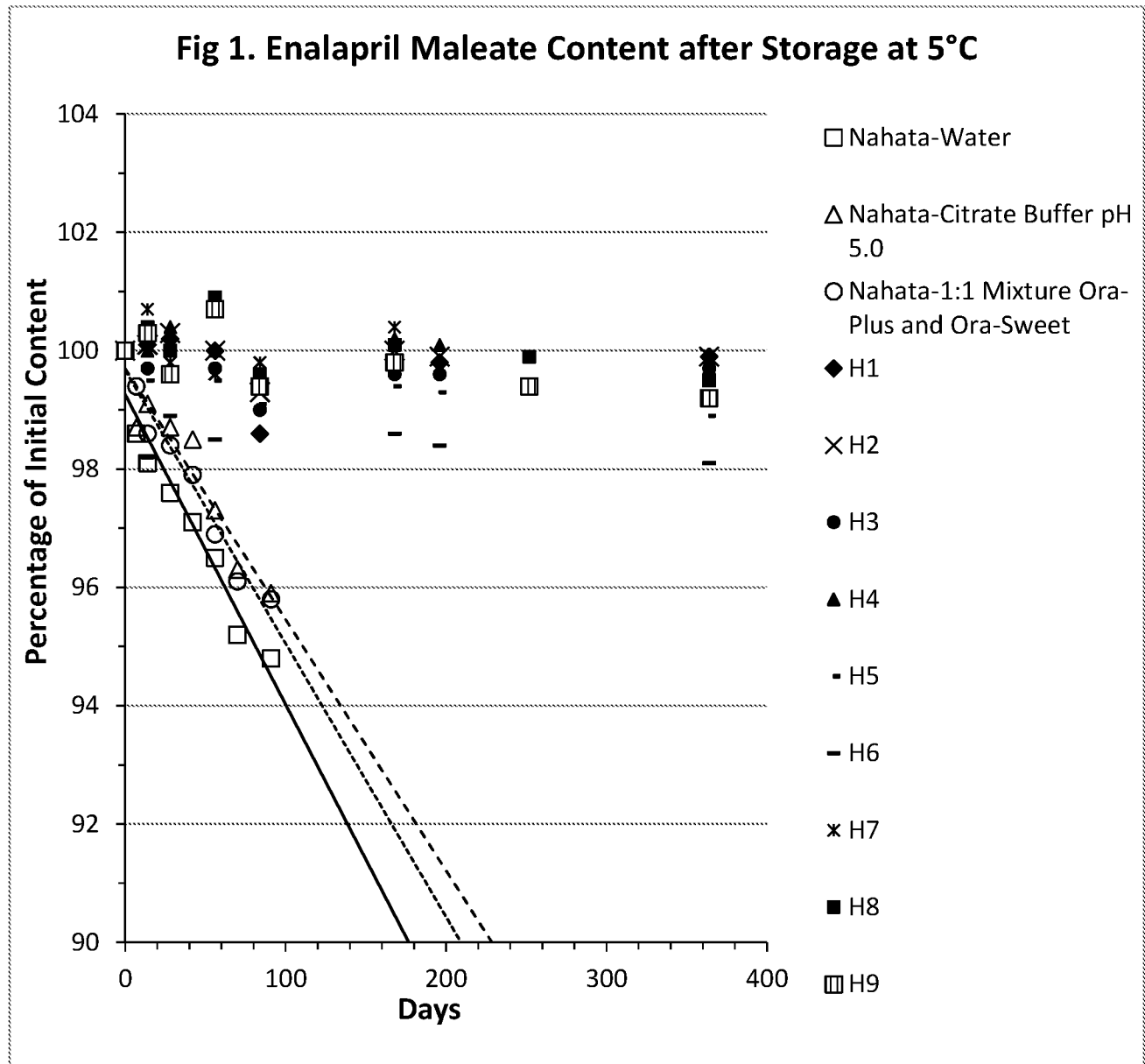
22. I have also reviewed Boukarim, which does not provide the stabilities of liquid enalapril formulations.

23. To compare the stability of the enalapril oral liquid formulations of the instant application with the extemporaneous preparations, such as those described in Nahata, the enalapril content of the Nahata formulations and that of formulations H1-H9 (stored at 5 °C) are provided in Table 5.

Table 5: Enalapril content in formulations after storage at 5 °C

Days	Nahata			Formulations of Instant Application								
	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	H1	H2	H3	H4	H5	H6	H7	H8	H9
0	100	100	100	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
7	98.6	98.7	99.4									
14	98.1	99.1	98.6	100.1	100.1	99.7	100.0	99.5	98.2	100.7	100.4	100.3
28	97.6	98.7	98.4	100.2	100.3	99.6	100.4	100.0	98.9	99.8	100.0	99.6
42	97.1	98.5	97.9									
56	96.5	97.3	96.9	100.0	100.0	99.7	100.0	99.5	98.5	99.6	100.9	100.7
70	95.2	96.3	96.1									
84				98.6	99.3	99.0	99.5	99.1	99.4	99.8	99.6	99.4
91	94.8	95.9	95.8									
168				99.8	100.0	99.6	100.2	99.4	98.6	100.4	100.1	99.8
196				99.8	99.9	99.6	100.1	99.3	98.4	99.7		
252											99.9	99.4
364				99.9	99.9	99.7	99.7	98.9	98.1	99.8	99.5	99.2

24. To further describe the contrast in stability, the enalapril concentrations published by Nahata, and the concentrations from H1-H9 are plotted graphically in Figure 1 with linear regression of the data for extrapolation.




25. Table 5 and Figure 1 show that formulations H1 to H9 exhibit excellent stability for at least 12 months (52 weeks) at 5 °C with essentially no or little loss of enalapril content, in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at about 5 °C for more

than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.

26. The enalapril content and total impurity data submitted in Tables 1-5 and Figure 1 show that the formulations of the present application are significantly more stable than the extemporaneously prepared formulations. Further, as shown by the stability of formulations H1-H9 and formulations of Table 3, a variety of buffers, which are capable of maintaining the pH values of the formulations at about or below 4.5, can be used in the formulations of the present application.

27. I declare that all statements made herein are true to the best of my knowledge, or if made upon information and belief, are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted on this 14th day of May, 2020



Gerold L. Mosher, Ph.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 1032
Serial No.: 16/242,898	Examiner: SPRINGER, Stephanie K
Filed: January 8, 2019	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on May 14, 2020, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: _____/Paula Derby /</p>

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**RESPONSE TO FINAL OFFICE ACTION DATED NOVEMBER 19, 2019, WITH
REQUEST FOR CONTINUED EXAMINATION**

Commissioner:

Applicant hereby submits a response to the Final Office Action dated November 19, 2019 (the “Office Action”), in the above-identified application. Applicant respectfully requests reconsideration and allowance of the pending claims.

This response is submitted with a petition to obtain a three-month extension-of-time, extending the deadline for responding to May 19, 2020. Accordingly, this response is timely filed. Commissioner is hereby authorized to charge any fees associated with filing of this response, to Deposit Account No. 23-2415, referencing Docket No. 43060-707.305.

Amendments to the Claims, reflecting the status of the claims, begin on page 2.

Remarks begin on page 7.

Conclusion begins on page 14.

Amendments to the Claims

This listing of claims will replace all prior versions, amendments, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicant reserves the right to pursue the subject matter of the withdrawn claims in this or any other appropriate patent application.

Listing of the Claims:

1. (Currently amended) A stable oral liquid formulation, ~~comprising~~ consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
 wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and
 wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
2. (Currently amended) The stable oral liquid formulation of claim 1, ~~further~~ comprising a sweetener.
3. (Original) The stable oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. (Currently amended) The stable oral liquid formulation of claim 1, ~~further~~ comprising a flavoring agent.
5. (Previously presented) The stable oral liquid formulation of claim 1, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, or a tartrate buffer.

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6. (Original) The stable oral liquid formulation of claim 1, wherein the buffer comprises citric acid and sodium citrate.
7. (Original) The stable oral liquid formulation of claim 6, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.
8. (Canceled)
9. (Currently amended) The stable oral liquid formulation of claim 1, wherein the buffer concentration is about 10[[5]] mM to about 20 mM.
10. (Original) The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH between about 3 and about 4.
11. (Original) The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH at about 3.3.
12. (Original) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 18 months.
13. (Original) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 24 months.
14. (Currently amended) A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;
 wherein the formulation ~~optionally~~ comprises a sweetener and[[/or]] a flavoring agent, wherein the formulation ~~and~~ is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 12 months; and
 wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
15. (Currently amended) A stable oral liquid formulation, ~~comprising~~ consisting essentially of:

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- (i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
 - (iii) about 19% (w/w of solids) of a preservative that is sodium benzoate; and
 - (iv) water;
- wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
- wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months; and
- wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

16. (Currently amended) The stable oral liquid formulation of claim 15, ~~further~~ comprising a sweetener.
17. (Original) The stable oral liquid formulation of claim 16, wherein the sweetener is sucralose.
18. (Currently amended) The stable oral liquid formulation of claim 15, ~~further~~ comprising a flavoring agent.
19. (Currently amended) The stable oral liquid formulation of claim 15, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.
20. (Original) The stable oral liquid formulation of claim 15, wherein the buffer comprises citric acid and sodium citrate.
21. (Original) The stable oral liquid formulation of claim 20, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.
22. (Canceled)
23. (Canceled)
24. (Currently amended) The stable oral liquid formulation of claim 15, wherein the buffer concentration is about 10[[5]] mM to about 20 mM.

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25. (Original) The stable oral liquid formulation of claim 15, wherein the buffer maintains the pH between about 3 and about 3.5.
26. (Original) The stable oral liquid formulation of claim 15, wherein the buffer maintains the pH at about 3.3.
27. (Original) The stable oral liquid formulation of claim 15, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 18 months.
28. (Original) The stable oral liquid formulation of claim 15, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 24 months.
29. (Currently amended) A stable oral liquid formulation, ~~comprising~~ consisting essentially of:
- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a citrate buffer to maintain the pH about 4.5 or below comprising citric acid and sodium citrate;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;
- wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
- wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and
- wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
30. (Original) The stable oral liquid formulation of claim 29, wherein the citric acid and/or the sodium citrate is anhydrous, monohydrate or dihydrate.
31. (New) The stable oral liquid formulation of claim 1, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.
32. (New) The stable oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.

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33. (New) The stable oral liquid formulation of claim 1, wherein the buffer comprises a buffer selected from a citrate, a phosphate, a citrate/phosphate, an acetate, a tartrate, a lactate, a glycinate, and an amino acid buffer.

* * *

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REMARKS

Before entry of the instant amendments, claims 1-7, 9-22, and 24-30 were pending.

By way of the instant amendments, claims 1, 2, 4, 9, 14-16, 18, 19, 24 and 29 have been amended, claim 22 has been canceled, and new claims 31-33 are added. Support for the amendments is in the application and claims as originally filed, see, e.g., original claims 2-4, paragraphs [0036]-[0036], [0058], [0066], [0076], Example E and Table E-2 of the published application. No new matter has been added.

Upon entry of the amendments, claims 1-7, 9-21, 24-33 are pending and under examination. Reconsideration and allowance is respectfully requested in light of the following remarks.

The §103 Rejection

Claims 1-7, 9-22, and 24-30 were rejected under 35 U.S.C. 103 as obvious over Nahata et al., “Stability of enalapril maleate in three extemporaneously prepared oral liquids,” Am. J. Health-Syst. Pharm., 1998, vol. 55, pages 1155-1157 (cited in IDS) (“Nahata”) in view of Sosnowska et al., “Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared From Commercially Available Tablets,” Acta Poloniae Pharmaceutica - Drug Research, 2009, vol. 66, no. 3, pages 321-326 (cited in PTO-892) (“Sosnowska”) in view of Boukarim et al., “Preservatives in Liquid Pharmaceutical Preparations”, J. Appl. Res., 2009, vol. 9, no. 1&2, pages 14-17 (cited in PTO-892) (“Boukarim”).

The Office admits that “Nahata and Sosnowska do not explicitly teach that the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months.” However, the Office nevertheless alleges “the combined teachings of Nahata, Sosnowska, and Boukarim meet the instantly claimed requirements, and absent evidence to the contrary, one would expect the composition to have the same properties as instantly claimed.” Page 11 of the Office Action.

Applicant respectfully submits that none of the three cited references—Nahata, Sosnowska, and Boukarim—teaches or suggests all the elements of the claimed formulations,

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e.g., the stability element, that is “the formulation is stable at 5 ± 3 °C for at least 12 months,” is not disclosed or suggested. The superior stability is unexpected in view of cited art.

Applicant further submits an Inventor Declaration by Dr. Gerold Mosher dated May, 14, 2020 (the “Mosher Declaration”), with evidence to overcome the §103 rejections asserted by the Office, as discussed in greater detail below.

a. The Cited References Do Not Teach or Suggest Enalapril Oral Liquid Formulations That Are Stable at 5 ± 3 °C For At Least 12 Months

To establish a prima facie case of obviousness, the cited art itself or “the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]” at the time of the invention are to have taught or suggested the claim elements. *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007). The Examiner must make “a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art.” *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995). As such, “obviousness requires a suggestion of all limitations in a claim.” *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

None of Nahata, Sosnowska, and Boukarim teaches or suggests enalapril oral liquid formulations that are stable at 5 ± 3 °C for at least 12 months, which is one of the elements in the present claims. Specifically, the amended claim 1 is directed to a stable oral liquid formulation consisting essentially of:

- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
 - (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
 - (iv) water;
- wherein the formulation optionally comprises a sweetener, a flavoring agent, or both; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

Claims 14, 15 and 29 similarly recite formulations that comprise the stability element.

The Specification and Drawings of the instant application provide support and evidence of this stability; for example, Table E-2 depicts very little amounts of diketopiperazine or enalaprilat degradants formed in formulations E1 to E6 when stored at 5 °C. Table E-1 shows that formulations E1 to E6 contain enalapril, a buffer (e.g., citric acid and sodium citrate at a concentration of 5 mM, 10 mM, or 20 mM) that maintains the pH at 4.5 or below, a preservative that is sodium benzoate, and water, which represent some of the embodiments of the claimed formulation.

Moreover, the Mosher Declaration provides additional exemplary formulations that are prepared with a variety of buffers, including citrate, phosphate, citrate/phosphate, acetate, glycinate, fumarate, tartrate, malate, aspartate, lactate, formate, phthalate, acetate, succinate, gluconate, and glutamate buffers, and the formulations exhibit superior stability. Specifically, in the Mosher Declaration, Dr. Mosher provided 52-week stability data for exemplary formulations of Table 1, which include formulations made with sodium citrate, citric acid, phosphate, citrate/phosphate, acetate, glycine, and tartrate buffers of the present disclosure. Dr. Mosher also provided the stability results of additional exemplary formulations in Table 3 (with fumarate, tartrate, malate, aspartate, glycinate, lactate, formate, phthalate, acetate, succinate, gluconate, glutamate, citrate, phosphate, and citrate/phosphate buffers) under an accelerated condition of 60 °C for 7 days.

Dr. Mosher explains: “Tables 1-4 show that the formulations of the ’998 application can be prepared using a variety of buffers (e.g., citrate, phosphate, citrate/phosphate, acetate, glycinate, fumarate, tartrate, malate, aspartate, lactate, formate, phthalate, acetate, succinate, gluconate, and glutamate buffers) and the pH values of the formulations can vary, e.g., at least from about 3 to about 4.5. All the formulations in Tables 1 and 3 demonstrated superior stability—retaining greater than 98% of the initial enalapril maleate content and having less than 2% w/w total impurity after 52 weeks at 5 °C, or having comparable stability when tested under an accelerated condition of 60 °C.” Mosher Declaration, ¶18.

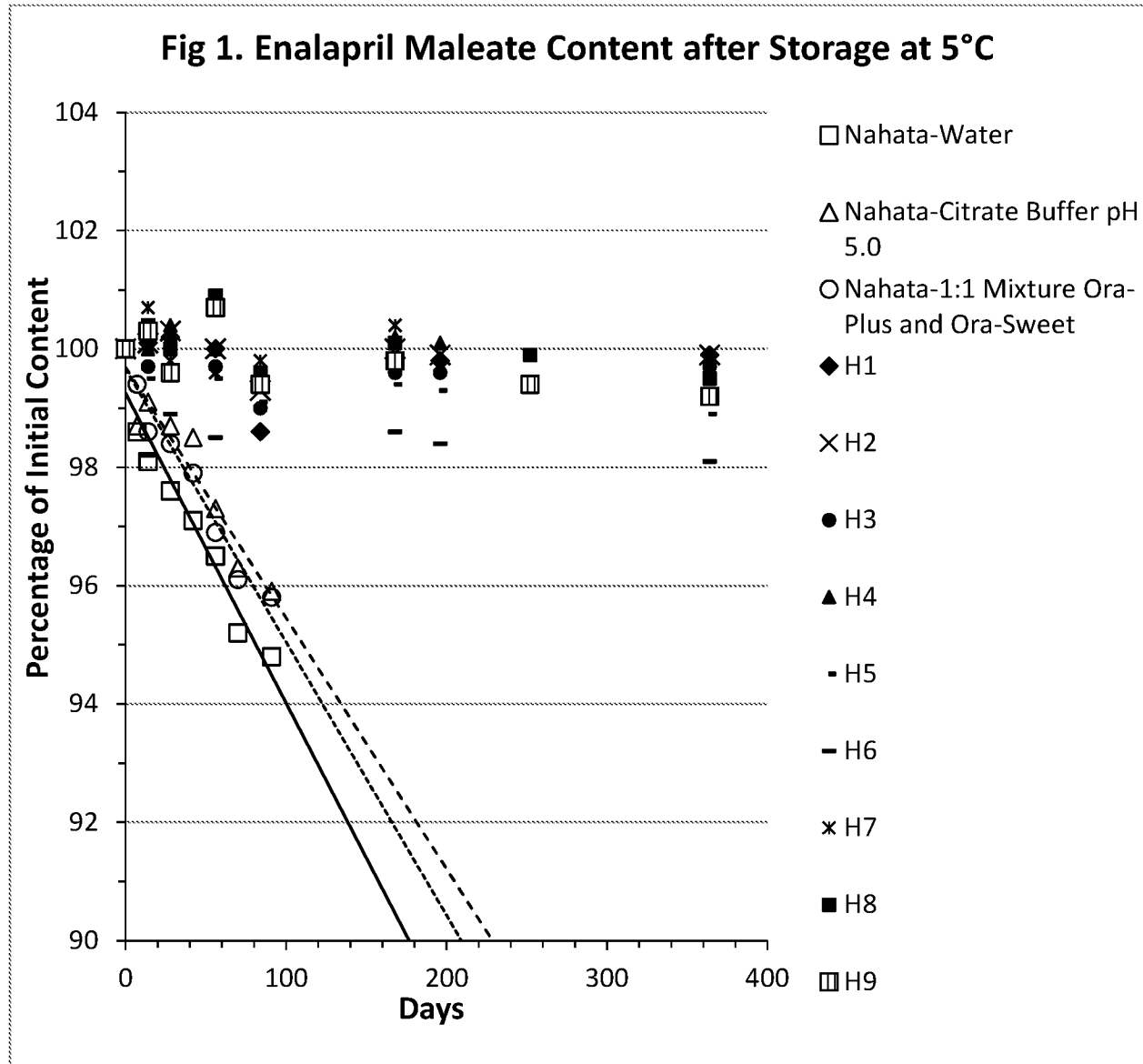
To illustrate the dramatic differences in stability between the enalapril oral liquid formulations of the present application with the stability of the enalapril liquid preparation in Nahata, Dr. Mosher plotted graphically with linear regression of the data for extrapolation of the

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available refrigerated (5 °C) stability data published by Nahata as well as formulations H1-H9 of Table 1, which are exemplary formulations of the present application. The stability comparisons at 5 °C are presented in Table 5 and Fig 1., and Fig.1 is provided below. *See*, Mosher Declaration, ¶¶23-25.



As Dr. Mosher explains, “Table 5 and Figure 1 show that formulations H1 to H9 exhibit excellent stability for at least 12 months (52 weeks) at 5 °C with essentially no or little loss of enalapril content, in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not

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disclose stability at about 5 °C for more than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.” Mosher Declaration, ¶25. Evidently, remaining stable for at least 12 months at 5 ± 3 °C is not an inherent property of the Nahata formulations.

Sosnowska similarly discloses extemporaneously prepared formulations. Sosnowska teaches liquid formulations of enalapril prepared from crushed enalapril tablets. *See*, page 322 of Sosnowska. “[I]n the absence of microbiological data, the shelf-life given to extemporaneous products containing preservatives is usually 30 days - the time period in which the formulations were tested.” *See*, Table 1 and page 325 of Sosnowska. Accordingly, Sosnowska does not disclose or suggest stability beyond 30 days for the extemporaneous preparations.

Further, Applicant respectfully points out that formulations of the present disclosure have overcome limitations of the extemporaneously prepared formulations. As Dr. Mosher explains, “[t]raditionally, approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in ‘Nahata’ and subsequently administering the suspension to the patient, or (3) reconstituting a powder in a liquid carrier . . . For the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination.” Mosher Declaration, ¶10-11. The stable enalapril oral liquid formulations in the present application represent an elegant solution over the previous methods of obtaining liquid enalapril formulation.

Thus, the data presented in the Mosher Declaration clearly demonstrates extemporaneous preparations, such as the preparations disclosed in Nahata and Sosnowska, do not meet the stability requirement of the present claims. As for Boukarim, it does not disclose any enalapril oral liquid formulation or any stability thereof.

As such, none of the cited references—Nahata, Sosnowska, and Boukarim—discloses or suggests any liquid formulations of enalapril that is stable **at about 5 ± 3 °C for at least 12 months**, either explicitly or by inherency. Accordingly, Applicant respectfully requests the §103 rejections be withdrawn.

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b. Unexpected Results

The presence of an unexpected property is evidence of nonobviousness. *See*, MPEP § 716.02. Evidence of unexpected results must be weighed against evidence supporting prima facie obviousness in making a final determination of the obviousness of the claimed invention. *See*, *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978); MPEP § 716.02.

Applicant submits that the superior stability yielded by the claimed formulations are unexpected in view of the cited art.

As explained in the Mosher Declaration, the claimed stable enalapril liquid formulations are dramatically more stable than extemporaneously prepared enalapril formulations. In the Mosher Declaration, Dr. Mosher plotted graphically, with linear regression of the data for extrapolation of the stability data published in Nahata, as well as corresponding enalapril formulations H1-H9, which are exemplary formulations of the instant application. *See*, Mosher Declaration, Fig. 1.

Formulations H1-H9 were prepared with a variety of buffers including sodium citrate, citric acid, phosphate, citrate/phosphate, acetate, glycine, and tartrate. As evidenced by Fig. 1, formulations H1-H9 demonstrate essentially no loss of enalapril for at least 12 months at 5 °C. These results drastically contrast with the stability or lack thereof in the extemporaneous enalapril preparations, where the enalapril degrades substantially after initial preparation. At about 90-100 days, the extemporaneous preparations are at about 95% of the starting enalapril concentration when stored at 4 °C.

Further, Dr. Mosher provided an accelerated stability test under 60 °C, which shows that formulations prepared with a variety of buffers, including fumarate, tartrate, malate, aspartate, glycinate, lactate, formate, phthalate, acetate, succinate, gluconate, glutamate, citrate, phosphate, and citrate/phosphate buffers, have comparable and superior stability. Mosher Declaration, ¶16, Table 3, and Table 4.

These unexpected stability results of the presently claimed formulations are not taught by, and could not have been predicted or contemplated by Nahata, Sosnowska, or Boukarim.

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Indeed, as Dr. Mosher explains, “the extrapolated lines [in Nahata] show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.” Mosher Declaration, ¶25. Thus, one of ordinary skill in the art would not reasonably expect, based on the teachings in Nahata, to make a formulation that is stable at about 5 ± 3 °C for a period that is more than three times longer than the Nahata formulation.

Similarly, Sosnowska does not show any stability data beyond 30 days. When stored at 4 °C, Sosnowska formulations with an initial enalapril concentration at about 1.0 mg/mL contained only about 98% initial enalapril concentration at the end of the 30-day period. One of ordinary skill in the art would not reasonably expect, based on the teachings in Sosnowska, to make a formulation that is stable at about 5 ± 3 °C for at least 365 days.

Further, none of the references provide any teachings or suggestions to arrive at the instantly claimed stable oral liquid formulation that yields the unexpected, superior stability. For example, the extemporaneously prepared formulation in Nahata contains about 19 components in addition to enalapril and water. However, Nahata does not provide any expectation that any particular combination would be successful for making a stable enalapril oral liquid formulation, which can extend the stability from less than 100 days to at least 12 months at 5 °C. Similarly, Sosnowska fails to provide any expectation or suggestion that any modification of the components can lead to a stable oral liquid formulation that is stable at about 5 ± 3 °C for at least 12 months (that is 12 times longer than the stability period shown in Sosnowska).

Thus, the instantly claimed formulations have unexpected, superior stability results.

Accordingly, Applicant respectfully requests the §103 rejection be withdrawn for at least the reasons stated above. Applicant believes that the Application is in condition for allowance and such action is earnestly solicited.

* * *

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CONCLUSION

Applicant submits that this response fully addresses the Office Action dated November 19, 2019. Applicant believes that for the reasons set forth herein the pending claims are in condition for allowance and early and favorable consideration is respectfully requested.

Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (617) 598-7823.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: May 14, 2020

By: /Clark Lin/
Clark Y. Lin, Ph.D., Esq.
Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (617) 598-7823
Customer No. 021971

Attorney Docket No. 43060-707.305
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	MOSHER; Gerold L. et al.	Group Art Unit:	1629
Serial Number:	16/242,898	Examiner:	SPRINGER; Stephanie K.
Filing or 371 (c) Date:	2019-01-08	CONFIRMATION NO:	1032
Title:	ENALAPRIL FORMULATIONS		

FILED ELECTRONICALLY ON: June 5, 2020

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☒ *37 CFR § 1.97 (b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
-- OR --
 - ☐ (3) It is being filed before the mailing of a first Office action on the merits;
-- OR --
 - ☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☐ *37 CFR § 1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97 (e) provided concurrently herewith;
-- OR --
 - ☐ a fee of \$240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR § 1.97 (d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
-- AND --
 - ii. a fee of \$240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☐ *37 CFR §1.97 (e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
-- AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☐ *Statement Under 37 C.F.R. §1.704(d)*. Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☒ *37 CFR §1.98 (a) (2)*. The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☐ *37 CFR §1.98(a)(3)*. The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
- OR --
- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☐ *37 CFR §1.98(d)*. Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.43060-707.305).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: June 5, 2020

By: /Clark Lin/
Clark Y. Lin, Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21,971



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 08/03/2020
 WILSON, SONSINI, GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050

EXAMINER

RAO, SAVITHA M

ART UNIT

PAPER NUMBER

1629

DATE MAILED: 08/03/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/242,898	01/08/2019	Gerold L. MOSHER	43060-707.305	1032

TITLE OF INVENTION: ENALAPRIL FORMULATIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	11/03/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

21971 7590 08/03/2020
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/242,898	01/08/2019	Gerold L. MOSHER	43060-707.305	1032

TITLE OF INVENTION: ENALAPRIL FORMULATIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	11/03/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	514-001000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/242,898	01/08/2019	Gerold L. MOSHER	43060-707.305	1032
21971	7590	08/03/2020	EXAMINER	
WILSON, SONSINI, GOODRICH & ROSATI			RAO, SAVITHA M	
650 PAGE MILL ROAD			ART UNIT	
PALO ALTO, CA 94304-1050			PAPER NUMBER	
			1629	
DATE MAILED: 08/03/2020				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/242,898	Applicant(s) MOSHER et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 05/14/2020.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 1-7,9-21 and 24-33. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. <input type="checkbox"/> Notice of References Cited (PTO-892) 2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>06/05/2020</u> . 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. <input checked="" type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date. <u>07/01/2020</u> .	5. <input type="checkbox"/> Examiner's Amendment/Comment 6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance 7. <input type="checkbox"/> Other _____.
--	--

/SAVITHA M RAO/
Primary Examiner, Art Unit 1629

Application/Control Number: 16/242,898
Art Unit: 1629

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Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-7, 9-21 and 24-33 are pending in the instant application.

Applicants representative Mr. Clark Lin interviewed with the examiner to discuss the claim amendments and the submitted affidavit on 7/1/2020. Please see the attached interview summary for details.

Information Disclosure Statement

The information disclosure statement (IDS) dated 06/05/2020 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Terminal disclaimer

The terminal disclaimer filed on 08/01/2019 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **US patents 9669008, 9808442, 10039745 and 10154987 and US application 16/177159** have been reviewed and is accepted. The terminal disclaimer has been recorded.

Rule 37 CFR 1.132 Declaration

Applicant's submission of the declarations of Gerold Mosher under 37 CFR 1.132 filed 05/15/2020 is acknowledged. The declarations is found to be persuasive in

Application/Control Number: 16/242,898

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Art Unit: 1629

overcoming the outstanding rejections set forth in the non-final rejection dated 01/07/2020.

REASONS FOR ALLOWANCE

In view of the applicants claim amendments, arguments and the declaration filed on 05/14/2020 and the following examiners statement of reasons for allowance, claims 1-7, 9-21 and 24-33 are found to be allowable.

Following a diligent search it was determined that the prior art neither teaches nor provides adequate motivation to arrive at the instantly claimed stable oral liquid formulation, consisting essentially of: (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof, (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM; (iii) about 1 mg/ml of a preservative that is sodium benzoate; and (iv) water; wherein the formulation optionally comprises a sweetener, a flavoring agent, or both; wherein the formulation is stable at about 5 ± 30 C for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period..

Conclusion

Claims 1-7, 9-21 and 24-33 (renumbered as 1-30) are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably

Application/Control Number: 16/242,898

Page 4

Art Unit: 1629

accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA M RAO/
Primary Examiner, Art Unit 1629

<i>Applicant-Initiated Interview Summary</i>	Application No. 16/242,898	Applicant(s) MOSHER et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	AIA (FITF) Status Yes

All participants (applicant, applicants representative, PTO personnel):

(1) SAVITHA M. RAO. (3) ____.

(2) Clark Lin. (4) ____.

Date of Interview: 01 July 2020.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: ____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1.

Identification of prior art discussed: none.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicants discussed the claim amendments and how that overcomes the rejection on file.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/SAVITHA M RAO/ Primary Examiner, Art Unit 1629	
--	--

Summary of Record of Interview Requirements**Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record**

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews

Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

21971 7590 08/03/2020
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650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Erin Dugan	(Typed or printed name)
/erin dugan/	(Signature)
August 7, 2020	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/242,898	01/08/2019	Gerold L. MOSHER	43060-707.305	1032

TITLE OF INVENTION: ENALAPRIL FORMULATIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	11/03/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	514-001000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

Wilson, Sonsini, Goodrich
& Rosati, P.C.

1

2

3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

Silvergate Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Greenwood Village, CO

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 23-2415

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Clark Lin/

Date August 7, 2020

Typed or printed name Clark Lin, Ph.D., J.D.

Registration No. 67,024



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/242,898	09/15/2020	10772868	43060-707.305	1032

21971 7590 08/26/2020

WILSON, SONSINI, GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Gerold L. MOSHER, Kansas City, MO;
 Silvergate Pharmaceuticals, Inc., Greenwood Village, CO;
 David W. MILES, Kansas City, MO;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

PTO/AIA/15 (10-17)

Approved for use through 11/30/2020. OMB 0651-0032

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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UTILITY PATENT APPLICATION TRANSMITTAL <i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i>		Attorney Docket No. 43060-707.304	
		First Named Inventor Gerold L. MOSHER	
		Title ENALAPRIL FORMULATIONS	
		Priority Mail Express® Label No. Filed Electronically via EFS-Web on October 31, 2018	

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
<ol style="list-style-type: none"> 1. <input type="checkbox"/> Fee Transmittal Form (PTO/SB/17 or equivalent) 2. <input type="checkbox"/> Applicant asserts small entity status. See 37 CFR 1.27 3. <input type="checkbox"/> Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. <input checked="" type="checkbox"/> Specification [Total Pages <u>52</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. <input checked="" type="checkbox"/> Drawing(s) (35 U.S.C. 113) [Total Sheets <u>2</u>] 6. Inventor's Oath or Declaration [Total Pages <u>2</u>] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) <ol style="list-style-type: none"> a. <input type="checkbox"/> Newly executed (original or copy) b. <input checked="" type="checkbox"/> A copy from a prior application (37 CFR 1.63(d)) 7. <input checked="" type="checkbox"/> Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) <div style="margin-left: 20px;"> <input type="checkbox"/> Landscape Table on CD </div> 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) <ol style="list-style-type: none"> a. <input type="checkbox"/> Computer Readable Form (CRF) b. <input type="checkbox"/> Specification Sequence Listing on: <ol style="list-style-type: none"> i. <input type="checkbox"/> CD-ROM or CD-R (2 copies); or ii. <input type="checkbox"/> Paper c. <input type="checkbox"/> Statements verifying identity of above copies 	ACCOMPANYING APPLICATION PAPERS <ol style="list-style-type: none"> 10. <input type="checkbox"/> Assignment Papers (cover sheet & document(s)) Name of Assignee _____ 11. <input checked="" type="checkbox"/> 37 CFR 3.73(c) Statement <input checked="" type="checkbox"/> Power of Attorney (when there is an assignee) 12. <input type="checkbox"/> English Translation Document (if applicable) 13. <input type="checkbox"/> Information Disclosure Statement (PTO/SB/08 or PTO-1449) <div style="margin-left: 20px;"><input type="checkbox"/> Copies of citations attached</div> 14. <input type="checkbox"/> Preliminary Amendment 15. <input type="checkbox"/> Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. <input type="checkbox"/> Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. <input type="checkbox"/> Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 18. <input checked="" type="checkbox"/> Other: Certification and Request for Prioritized Examination Under 37 CFR 1.102(e) - 1 pp. _____ _____ _____

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
 (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS				
<input checked="" type="checkbox"/> The address associated with Customer Number: <u>21971</u> OR <input type="checkbox"/> Correspondence address below				
Name				
Address				
City	State	Zip Code		
Country	Telephone	Email		

Signature	/Celine Bonnefous/	Date	October 31, 2018
Name (Print/Type)	Celine M. Bonnefous	Registration No. (Attorney/Agent)	72875

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

SLVGT-EPA_0105687

Doc Code: TRACK1.REQ

Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Gerold L. MOSHER	Nonprovisional Application Number (if known):	
Title of Invention:	ENALAPRIL FORMULATIONS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

- The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
- I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
- The applicable box is checked below:

I. ☒ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

- (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.
---OR---
(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.
- An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, or the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

- A request for continued examination has been filed with, or prior to, this form.
- If the application is a utility application, this certification and request is being filed via EFS-Web.
- The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
- This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
- No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

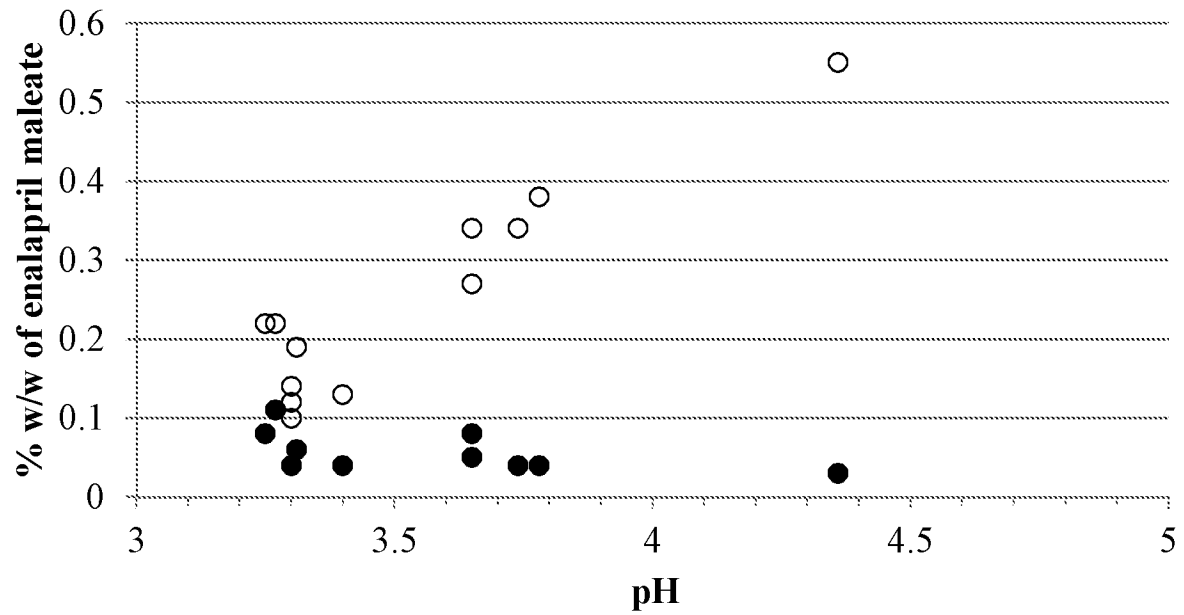
Signature	/Celine Bonnefous/	Date	October 31, 2018
Name (Print/Typed)	Celine M. Bonnefous	Practitioner Registration Number	72875
<p>Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.*</p>			
<p><input checked="" type="checkbox"/> *Total of <u>1</u> forms are submitted.</p>			

SLVGT-EPA_0105688

1/2

FIG. 1

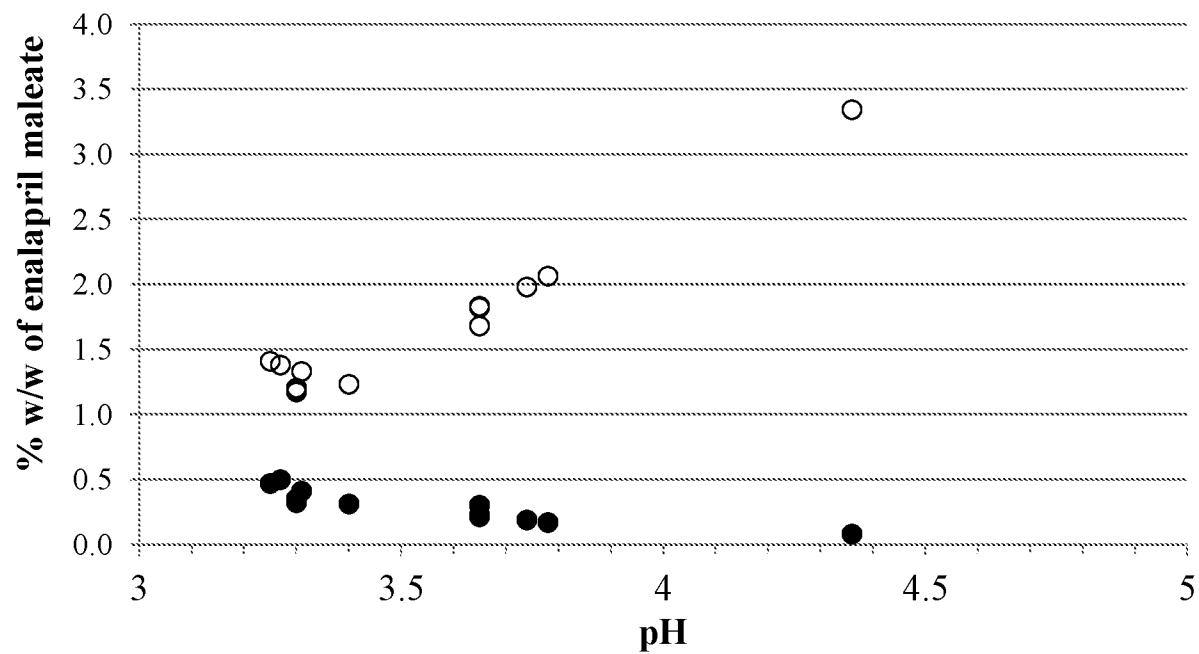
● Enalapril diketopiperazine; ○ Enalaprilat



2/2

FIG. 2

● Enalapril diketopiperazine; ○ Enalaprilat



ENALAPRIL FORMULATIONS

ABSTRACT OF THE DISCLOSURE

Provided herein are stable enalapril oral liquid formulations. Also provided herein are methods of using enalapril oral liquid formulations for the treatment of certain diseases including hypertension, heart failure and asymptomatic left ventricular dysfunction.

CLAIMS

WHAT IS CLAIMED IS:

1. A stable oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising citric acid and sodium citrate;
 - (iii) a preservative; and
 - (iv) water;wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
2. The stable oral liquid formulation of claim 1 further comprising a sweetener.
3. The stable oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. The stable oral liquid formulation of claim 1 further comprising a flavoring agent.
5. The stable oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
6. The stable oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
7. The stable oral liquid formulation of claim 1, wherein the buffer comprises about 0.8 to about 3.5 mg/ml citric acid.
8. The stable oral liquid formulation of claim 1, wherein the buffer comprises about 0.1 to about 0.8 mg/ml sodium citrate.
9. The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is less than about 3.5.
10. The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.

11. The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is about 3.3.
12. The stable oral liquid formulation of claim 1, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin.
13. The stable oral liquid formulation of claim 1, wherein the preservative is sodium benzoate.
14. The stable oral liquid formulation of claim 12, wherein the sodium benzoate is about 0.2 to about 1.2 mg/ml.
15. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 18 months.
16. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 24 months.
17. A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising citric acid and sodium citrate;
 - (iii) a preservative; and
 - (iv) water;wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
18. A stable oral liquid formulation, comprising:
 - (i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate;

(iii) about 1% to about 30% (w/w of solids) of a preservative; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

19. The stable oral liquid formulation of claim 18 further comprising a sweetener.
20. The stable oral liquid formulation of claim 19, wherein the sweetener is sucralose.
21. The stable oral liquid formulation of claim 18 further comprising a flavoring agent.
22. The stable oral liquid formulation of claim 18, wherein the formulation does not contain mannitol.
23. The stable oral liquid formulation of claim 18, wherein the formulation does not contain silicon dioxide.
24. The stable oral liquid formulation of claim 18, wherein the pH of the stable oral liquid formulation is less than about 3.5.
25. The stable oral liquid formulation of claim 18, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.
26. The stable oral liquid formulation of claim 18, wherein the pH of the stable oral liquid formulation is about 3.3.
27. The stable oral liquid formulation of claim 18, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin.
28. The stable oral liquid formulation of claim 18, wherein the preservative is sodium benzoate.

29. The stable oral liquid formulation of claim 18, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 18 months.
30. The stable oral liquid formulation of claim 18, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 24 months.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.304
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.</p> <p>This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

Secrecy Order 37 CFR 5.2:

<input type="checkbox"/>	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
--------------------------	---

Inventor Information:

Inventor	1	Remove		
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Gerold	L.	MOSHER	
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service				
City	Kansas City	State/Province	MO	Country of Residence
				US

Mailing Address of Inventor:

Address 1	12215 Avila Drive			
Address 2				
City	Kansas City	State/Province	MO	
Postal Code	64145	Country	US	

Inventor	2	Remove		
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	David	W.	MILES	
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service				
City	Kansas City	State/Province	MO	Country of Residence
				US

Mailing Address of Inventor:

Address 1	12309 Wyandotte Street			
Address 2				
City	Kansas City	State/Province	MO	
Postal Code	64145	Country	US	

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

[Add](#)**Correspondence Information:**

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

SLVGT-EPA_0105706

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.304
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

☐ An Address is being provided for the correspondence information of this application.

Customer Number	21971		
Email Address	patentdocket@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	ENALAPRIL FORMULATIONS		
Attorney Docket Number	43060-707.304	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	2	Suggested Figure for Publication (if any)	1

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	<input type="radio"/> US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	21971		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.304
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
	Continuation of	16/003994	2018-06-08		
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/003994	Continuation of	15802341	2017-11-02	10039745	2018-08-07
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/802341	Continuation of	15/613622	2017-06-05	9808442	2017-11-07
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/613622	Continuation of	15/081603	2016-03-25	9669008	2017-06-06
Prior Application Status	Expired	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
15/081603	Claims benefit of provisional	62/310198	2016-03-18		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.					

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove			
Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ^j (if applicable)
			SLVGT-EPA_0105708

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.304
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

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Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.304
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.304
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant	1	Remove
<p>If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.</p> <p style="text-align: right;">Clear</p>		
<input checked="" type="radio"/> Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
<div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
Name of the Deceased or Legally Incapacitated Inventor: <div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>		
Organization Name	Silvergate Pharmaceuticals, Inc.	
Mailing Address Information For Applicant:		
Address 1	6251 Greenwood Plaza Blvd., Bldg. 6, Suite 101	
Address 2		
City	Greenwood Village	State/Province
Country	US	Postal Code
Phone Number		Fax Number
Email Address		
Additional Applicant Data may be generated within this form by selecting the Add button. Add		

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.304
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Assignee	1			
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.				
				Remove
If the Assignee or Non-Applicant Assignee is an Organization check here.				<input type="checkbox"/>
Prefix	Given Name	Middle Name	Family Name	Suffix
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Mailing Address Information For Assignee including Non-Applicant Assignee:				
Address 1		<input type="text"/>		
Address 2		<input type="text"/>		
City	<input type="text"/>	State/Province	<input type="text"/>	
Country ⁱ	<input type="text"/>	Postal Code	<input type="text"/>	
Phone Number	<input type="text"/>	Fax Number	<input type="text"/>	
Email Address	<input type="text"/>			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.				Add

Signature:[Remove](#)

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Celine Bonnefous/		Date (YYYY-MM-DD)	2018-10-31
First Name	Celine	Last Name	Bonnefous	Registration Number
				72875
Additional Signature may be generated within this form by selecting the Add button.				Add

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.304
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

SLVGT-EPA_0105714

WSGR Docket No. 43060-707.304

PATENT APPLICATION
ENALAPRIL FORMULATIONS

Inventors: Gerold L. Mosher,
Citizen of the United States of America, Residing at
12215 Avila Drive
Kansas City, MO 64145

David W. Miles,
Citizen of the United States of America, Residing at
12309 Wyandotte Street
Kansas City, MO 64145

Assignees: Silvergate Pharmaceuticals, Inc.
6251 Greenwood Plaza Blvd., Bldg. 6, Suite 101
Greenwood Village, CO 80111

a Delaware Corporation

Entity: Large business concern



Wilson Sonsini Goodrich & Rosati
PROFESSIONAL CORPORATION

650 Page Mill Road
Palo Alto, CA 94304
(650) 493-9300 (Main)
(650) 493-6811 (Facsimile)

Filed Electronically on: October 31, 2018

ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

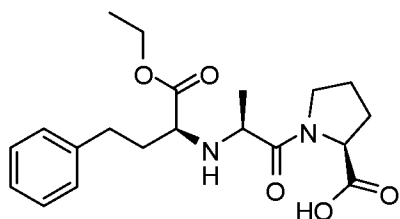
[0001] This application is a continuation of U.S. Patent Application No. 16/003,994, filed June 8, 2018, which is a continuation of U.S. Patent Application No. 15/802,341, filed November 2, 2017 (now U.S. Patent No. 10,039,745, issued August 7, 2018), which is a continuation of U.S. Patent Application No. 15/613,622, filed June 5, 2017 (now U.S. Patent No. 9,808,442, issued November 7, 2017), which is a continuation of U.S. Patent Application No. 15/081,603, filed March 25, 2016 (now U.S. Patent No. 9,669,008, issued June 06, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed March 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

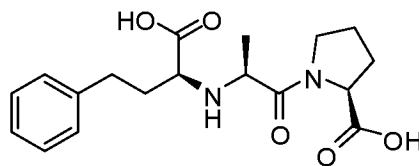
[0002] Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

[0003] A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

[0004] Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



Enalapril



Enalaprilat

[0005] Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

[0006] Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0007] In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25 % (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18 % (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47 % (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11 % (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25 % (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 18 months. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 24

months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0008] In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0009] In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 18 months. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0010] In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3 % (w/w of solids) enalapril maleate; (ii) about 13.5 % (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2 % (w/w of solids) citric acid; (iv) about 19.3 % (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0011] In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9 % (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 18 months. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0012] In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the

formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0013] Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0014] In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

[0015] Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0016] In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

[0017] Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments,

the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0018] Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

[0019] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0021] FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5°C.

[0022] FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22°C).

DETAILED DESCRIPTION OF THE INVENTION

[0023] Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

[0024] It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

[0025] Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

[0026] For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

[0027] Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

[0028] The present embodiments described herein provide a safe and effective oral administration of enalapril for the treatment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

[0029] As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in

the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

[0030] Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

[0031] Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

[0032] In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

[0033] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84

mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

[0034] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 % w/w to about 30 % w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 % w/w, about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 % w/w, about 14 % w/w, about 14.5 % w/w, about 15 % w/w, about 15.1 % w/w, about 15.2 % w/w, about 15.3 % w/w, about 15.4 % w/w, about 15.5 % w/w, about 15.6 % w/w, about 15.7 % w/w, about 15.8 % w/w, about 15.9 % w/w, about 16 % w/w, about 16.1 % w/w, about 16.2 % w/w, about 16.3 % w/w, about 16.4 % w/w, about 16.5 % w/w, about 16.6 % w/w, about 16.7 % w/w, about 16.8 % w/w, about 16.9 % w/w, about 17 % w/w, about 17.1 % w/w, about 17.2 % w/w, about 17.3 % w/w, about 17.4 % w/w, about 17.5 % w/w, about 17.6 % w/w, about 17.7 % w/w, about 17.8 % w/w, about 17.9 % w/w, about 18 % w/w, about 18.1 % w/w, about 18.2 % w/w, about 18.3 % w/w, about 18.4 % w/w, about 18.5 % w/w, about 18.6 % w/w, about 18.7 % w/w, about 18.8 % w/w, about 18.9 % w/w, about 19 % w/w, about 19.1 % w/w, about 19.2 % w/w, about 19.3 % w/w, about 19.4 % w/w, about 19.5 % w/w, about 19.6 % w/w, about 19.7 % w/w, about 19.8 % w/w, about 19.9 % w/w, about 20 % w/w, about 20.1 % w/w, about 20.2 % w/w, about 20.3 % w/w, about 20.4 % w/w, about 20.5 % w/w, about 20.6 % w/w, about 20.7 % w/w, about 20.8 % w/w, about 20.9 % w/w, about 21 % w/w, about 21.1 % w/w, about 21.2 % w/w, about 21.3 % w/w, about 21.4 % w/w, about 21.5 % w/w, about 21.6 % w/w, about 21.7 % w/w, about 21.8 % w/w, about 21.9 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5

% w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10 % w/w to about 25 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5 % w/w of the solids in the oral liquid formulation.

[0035] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1 % w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1 % w/w, about 0.15 % w/w, about 0.2 % w/w, about 0.25 % w/w, about 0.3 % w/w, about 0.35 % w/w, about 0.4 % w/w, about 0.45 % w/w, about 0.5 % w/w, about 0.55 % w/w, about 0.6 % w/w, about 0.65 % w/w, about 0.7 % w/w, about 0.75 % w/w, about 0.8 % w/w, about 0.85 % w/w, about 0.9 % w/w, about 0.95 % w/w, or about 1 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4 % w/w to about 0.7 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6 % w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

[0036] Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

[0037] Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate,

saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet AmTM liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet AmTM powder (Product Code 918.005--maltodextrin, sorbitol, and fructose combination and Product Code 918.010--water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweetTM (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), MaltisweetTM (maltitol solution, Ingredion), SorboTM (sorbitol and sorbitol/xylitol solution, SPI Polyols), InvertoseTM (high fructose corn syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

[0038] In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

[0039] In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

[0040] In some embodiments, sucralose is present in about 1 % w/w to about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about

13.5 % w/w, about 14% w/w, about 14.5 % w/w, about 15 % w/w, about 15.5 % w/w, about 16 % w/w, about 16.5 % w/w, about 17 % w/w, about 17.5 % w/w, about 18 % w/w, about 18.5 % w/w, about 19 % w/w, about 19.5 % w/w, about 20 % w/w, about 20.5 % w/w, about 21 % w/w, about 21.5 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5 % w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8 % w/w to about 18 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5 % w/w of the solids in the oral liquid formulation.

[0041] In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

[0042] In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

[0043] In some embodiments, xylitol is present in about 80 % w/w to about 99 % w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80 % w/w, about 81 % w/w, about 82 % w/w, about 83 % w/w, about 84 % w/w, about 85 % w/w, about 86 % w/w, about 87 % w/w, about 88 % w/w, about 89 % w/w, about 90 % w/w, about 91 % w/w, about 92 % w/w, about 93 % w/w, about 94 % w/w, about 95 % w/w, about 96 % w/w, about 97 % w/w, about 98 % w/w, or about 99 % w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96 % w/w to about 98 % w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96 % w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

[0044] Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

[0045] In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

[0046] In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

[0047] In some embodiments, the preservative is sodium benzoate.

[0048] In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

[0049] In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

[0050] In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about

1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

[0051] In some embodiments, sodium benzoate is present in about 1% w/w to about 30 % w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 % w/w, about 14 % w/w, about 14.5 % w/w, about 15 % w/w, about 15.1 % w/w, about 15.2 % w/w, about 15.3 % w/w, about 15.4 % w/w, about 15.5 % w/w, about 15.6 % w/w, about 15.7 % w/w, about 15.8 % w/w, about 15.9 % w/w, about 16 % w/w, about 16.1 % w/w, about 16.2 % w/w, about 16.3 % w/w, about 16.4 % w/w, about 16.5 % w/w, about 16.6 % w/w, about 16.7 % w/w, about 16.8 % w/w, about 16.9 % w/w, about 17 % w/w, about 17.1 % w/w, about 17.2 % w/w, about 17.3 % w/w, about 17.4 % w/w, about 17.5 % w/w, about 17.6 % w/w, about 17.7 % w/w, about 17.8 % w/w, about 17.9 % w/w, about 18 % w/w, about 18.1 % w/w, about 18.2 % w/w, about 18.3 % w/w, about 18.4 % w/w, about 18.5 % w/w, about 18.6 % w/w, about 18.7 % w/w, about 18.8 % w/w, about 18.9 % w/w, about 19 % w/w, about 19.1 % w/w, about 19.2 % w/w, about 19.3 % w/w, about 19.4 % w/w, about 19.5 % w/w, about 19.6 % w/w, about 19.7 % w/w, about 19.8 % w/w, about 19.9 % w/w, about 20 % w/w, about 20.1 % w/w, about 20.2 % w/w, about 20.3 % w/w, about 20.4 % w/w, about 20.5 % w/w, about 20.6 % w/w, about 20.7 % w/w, about 20.8 % w/w, about 20.9 % w/w, about 21 % w/w, about 21.1 % w/w, about 21.2 % w/w, about 21.3 % w/w, about 21.4 % w/w, about 21.5 % w/w, about 21.6 % w/w, about 21.7 % w/w, about 21.8 % w/w, about 21.9 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5 % w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5 % w/w of the solids in the oral liquid formulation.

[0052] In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1 % w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1 % w/w, about 0.15 % w/w, about 0.2 % w/w, about 0.25 % w/w, about 0.3 % w/w, about 0.35 % w/w, about 0.4 % w/w, about 0.45 % w/w, about 0.5 % w/w, about 0.55 % w/w, about 0.6 % w/w, about 0.65 % w/w, about 0.7 % w/w, about 0.75 % w/w, about 0.8 % w/w, about 0.85 % w/w, about 0.9 % w/w, about 0.95 % w/w, or about 1 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4 % w/w to about 0.7 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6 % w/w of the solids in the oral liquid formulation.

[0053] In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

[0054] In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

[0055] In some embodiments, the paraben or mixture of parabens is present in about 2 % w/w to about 30 % w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2 % w/w, about 3 % w/w, about 4 % w/w, about 5 % w/w, about 6 % w/w, about 7 % w/w, about 8 % w/w, about 9 % w/w, about 10 % w/w, about 11 % w/w, about 12 % w/w, about 13 % w/w, about 14 % w/w, about 15 % w/w, about 16 % w/w, about 17 % w/w, about 18 % w/w, about 19 % w/w, about 20 % w/w, about 21 % w/w, about 22 % w/w, about 23 % w/w, about 24 % w/w, about 25 % w/w, about 26 % w/w, about 27 % w/w, about 28 % w/w, about 29 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2 % w/w to about 3 % w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23 % w/w to about 26 % w/w of the

solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26 % w/w to about 30 % w/w of the solids in the oral liquid formulation.

Sweetener and preservative incompatibility

[0056] Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

[0057] In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

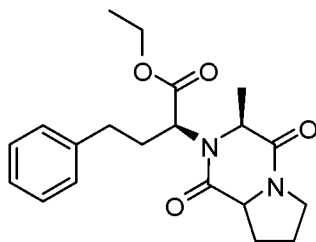
[0058] Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

[0059] In some embodiments, the oral liquid formulation comprises a buffer.

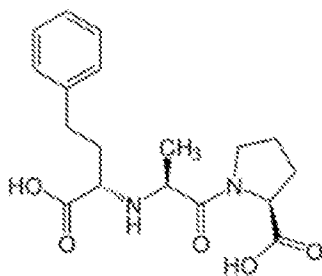
[0060] In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

[0061] In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

[0062] In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



enalapril diketopiperazine;



enalaprilat

[0063] In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

[0064] In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

[0065] In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

[0066] In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM,

about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

[0067] In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

[0068] In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1

mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

[0069] In some embodiments, citric acid is present in about 10 % w/w to about 50 % w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10 % w/w, about 11 % w/w, about 12 % w/w, about 13 % w/w, about 14 % w/w, about 15 % w/w, about 16 % w/w, about 17 % w/w, about 18 % w/w, about 19 % w/w, about 20 % w/w, about 21 % w/w, about 22 % w/w, about 23 % w/w, about 24 % w/w, about 25 % w/w, about 26 % w/w, about 27 % w/w, about 28 % w/w, about 29 % w/w, about 30 % w/w, about 31 % w/w, about 32 % w/w, about 33 % w/w, about 34 % w/w, about 35 % w/w, about 36 % w/w, about 37 % w/w, about 38 % w/w, about 39 % w/w, about 40 % w/w, about 41 % w/w, about 42 % w/w, about 43 % w/w, about 44 % w/w, about 45 % w/w, about 46 % w/w, about 47 % w/w, about 48 % w/w, about 49 % w/w, about 50 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19 % w/w of the solids in the oral liquid formulation.

[0070] In some embodiments, citric acid is present in about 1 % w/w to about 5 % w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1 % w/w, about 1.1 % w/w, about 1.2 % w/w, about 1.3 % w/w, about 1.4 % w/w, about 1.5 % w/w, about 1.6 % w/w, about 1.7 % w/w, about 1.8 % w/w, about 1.9 % w/w, about 2 % w/w, about 2.1 % w/w, about 2.2 % w/w, about 2.3 % w/w, about 2.4 % w/w, about 2.5 % w/w, about 2.6 % w/w, about 2.7 % w/w, about 2.8 % w/w, about 2.9 % w/w, about 3 % w/w, about 3.1 % w/w, about 3.2 % w/w, about 3.3 % w/w, about 3.4 % w/w, about 3.5 % w/w, about 3.6 % w/w, about 3.7 % w/w, about 3.8 % w/w, about 3.9 % w/w, about 4 % w/w, about 4.1 % w/w, about 4.2 % w/w, about 4.3 % w/w, about 4.4 % w/w, about 4.5 % w/w, about 4.6 % w/w, about 4.7 % w/w, about 4.8 % w/w, about 4.9 % w/w, or about 5 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6 % w/w of the solids in the oral liquid formulation.

[0071] In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid

formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/ml, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

[0072] In some embodiments, sodium citrate dihydrate is present in about 1 % w/w to about 15 % w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1 % w/w, about 1.1 % w/w, about 1.2 % w/w, about 1.3 % w/w, about 1.4 % w/w, about 1.5 % w/w, about 1.6 % w/w, about 1.7 % w/w, about 1.8 % w/w, about 1.9 % w/w, about 2 % w/w, about 2.1 % w/w, about 2.2 % w/w, about 2.3 % w/w, about 2.4 % w/w, about 2.5 % w/w, about 2.6 % w/w, about 2.7 % w/w, about 2.8 % w/w, about 2.9 % w/w, about 3 % w/w, about 3.1 % w/w, about 3.2 % w/w, about 3.3 % w/w, about 3.4 % w/w, about 3.5 % w/w, about 3.6 % w/w, about 3.7 % w/w, about 3.8 % w/w, about 3.9 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 % w/w, about 14 % w/w, about 14.5 % w/w, about 15 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5 % w/w of the solids

in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9 % w/w of the solids in the oral liquid formulation.

[0073] In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional excipients

[0074] In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

[0075] Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

[0076] In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

[0077] In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

[0078] Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches,

pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

[0079] Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, PA: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, PA: Mack Publishing Co 1975); Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, NY: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

[0080] The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

[0081] The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95 % or greater of the initial enalapril amount and about 5 % w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5 % w/w, about 4 % w/w, about 3 % w/w, about 2.5 % w/w, about 2 % w/w, about 1.5 % w/w, about 1 % w/w, or about 0.5 % w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1 % w/w total impurities or related substances.

[0082] At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5 ± 3 °C. In some embodiments, refrigerated condition is about 2 °C, about 2.1 °C, about 2.2 °C, about 2.3 °C, about 2.4 °C, about 2.5 °C, about 2.6 °C, about 2.7 °C, about 2.8 °C, about 2.9 °C, about 3 °C, about 3.1 °C, about 3.2 °C, about 3.3 °C, about 3.4 °C, about 3.5 °C, about 3.6 °C, about 3.7 °C, about 3.8 °C, about 3.9 °C, about 4 °C, about 4.1 °C, about 4.2 °C,

about 4.3 °C, about 4.4 °C, about 4.5 °C, about 4.6 °C, about 4.7 °C, about 4.8 °C, about 4.9 °C, about 5 °C, about 5.1 °C, about 5.2 °C, about 5.3 °C, about 5.4 °C, about 5.5 °C, about 5.6 °C, about 5.7 °C, about 5.8 °C, about 5.9 °C, about 6 °C, about 6.1 °C, about 6.2 °C, about 6.3 °C, about 6.4 °C, about 6.5 °C, about 6.6 °C, about 6.7 °C, about 6.8 °C, about 6.9 °C, about 7 °C, about 7.1 °C, about 7.2 °C, about 7.3 °C, about 7.4 °C, about 7.5 °C, about 7.6 °C, about 7.7 °C, about 7.8 °C, about 7.9 °C, or about 8 °C. At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. 25±5 °C; 55±10% RH). In some instances, an accelerated condition is at about 25 °C, about 30 °C, about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C or about 60 °C. In other instances, an accelerated condition is above 55% RH, about 65 % RH, about 70 % RH, about 75 % RH or about 80 % RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40 °C at 75±5 % RH humidity.

Enalapril Oral Powder Formulation

[0083] In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

[0084] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30 % w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 % w/w, about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 %

w/w, about 14% w/w, about 14.5 % w/w, about 15 % w/w, about 15.5 % w/w, about 16 % w/w, about 16.5 % w/w, about 17 % w/w, about 17.5 % w/w, about 18 % w/w, about 18.5 % w/w, about 19 % w/w, about 19.5 % w/w, about 20 % w/w, about 20.5 % w/w, about 21 % w/w, about 21.5 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5 % w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5 % w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5 % w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5 % w/w of the powder formulation. In some embodiments, enalapril is present in about 18 % w/w of the powder formulation.

[0085] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1 % w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1 % w/w, about 0.15 % w/w, about 0.2 % w/w, about 0.25 % w/w, about 0.3 % w/w, about 0.35 % w/w, about 0.4 % w/w, about 0.45 % w/w, about 0.5 % w/w, about 0.55 % w/w, about 0.6 % w/w, about 0.65 % w/w, about 0.7 % w/w, about 0.75 % w/w, about 0.8 % w/w, about 0.85 % w/w, about 0.9 % w/w, about 0.95 % w/w, or about 1 % w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4 % w/w to about 0.7 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6 % w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4 % w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5 % w/w of the powder formulation.

[0086] Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1 % w/w to about 30 % w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1 % w/w to about 30 % w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1 % w/w to about 30 % w/w of the solids in the oral liquid formulation, in an analogous enalapril

powder formulation sodium benzoate is present in about 1 % w/w to about 30 % w/w in the powder formulation.

[0087] Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

[0088] Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

[0089] In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

[0090] Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon

dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

[0091] In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

[0092] In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

[0093] In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

[0094] Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, PA: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, PA: Mack Publishing Co 1975); Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, NY: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

[0095] In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

[0096] Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof; and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2x10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

[0097] The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder

formulations having about 95 % or greater of the initial enalapril amount and 5 % w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5 % w/w, about 4 % w/w, about 3 % w/w, about 2.5 % w/w, about 2 % w/w, about 1.5 % w/w, about 1 % w/w, or about 0.5 % w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1 % w/w total impurities or related substances.

[0098] At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25 ± 4 °C; 55 ± 10 % RH). In some instances, an accelerated condition is at about 30 °C, about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C or about 60 °C. In other instances, an accelerated condition is above 65 % RH, about 70 % RH, about 75 % RH or about 80 % RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40 °C at 75 ± 5 % RH humidity.

Kits and Articles of Manufacture

[0099] For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

[00100] A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

[00101] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

[00102] Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

[00103] In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

[00104] In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described

herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

[00105] In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

[00106] In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

[00107] Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

[00108] In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but

can nevertheless be determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

[00109] In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76, mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

[00110] In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg,

about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

[00111] In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

[00112] In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

[00113] Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[00114] In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular

disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

[00115] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

[00116] In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00117] In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, *i.e.*, administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (*e.g.* drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

[00118] In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

[00119] In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10

minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

[00120] In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

[00121] The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

[00122] Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxybenzamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltiazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, losartan, eprosartin, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

[00123] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[00124] As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

[00125] The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[00126] “Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

[00127] As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

[00128] “Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

[00129] The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms “patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic

species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

[00130] By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[00131] The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[00132] A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

[00133] The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the

condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, “treat,” “treated,” “treatment,” or “treating” includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60 °C.

[00134] Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60 °C heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

[00135] The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at 60 °C	Formulation					
	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60 °C.

[00136] Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60 °C heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5mM citrate)	B2 (10mM citrate)	B3 (20mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7

Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

[00137] The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours at 60°C	Formulation		
	B1 (5mM citrate)	B2 (10mM citrate)	B3 (20mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives.

[00138] Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula[®] mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5 °C ± 3°C, at room temperature (19-23 °C) and at 40°C ± 2 °C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Powder Formulation (grams)					
Component	C1	C2	C3	C4	C5
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

[00139] The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	°C	Weeks	C1	C2	C3	C4	C5
Liquid Formulations							
Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
		4	0.02	0.03	0.03	0.03	0.02
		8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.04	0.02	0.02
		4	0.05	0.09	0.11	0.05	0.04
		8	0.08	0.17	0.19		
	40	0	0.03	0.04	0.04	0.02	0.02
		4	0.35	0.91	1.10	0.31	0.21
		8	0.65	1.80	2.05		
	5	0	0.18	0.14	0.12	0.13	0.19
		4	0.18	0.15	0.12	0.43	0.53
		8	0.55	0.38	0.34		
Enalaprilat	19-23	0	0.18	0.14	0.12	0.13	0.19
		4	1.35	0.83	0.80	1.75	2.29
		8	3.34	2.06	1.98		
	40	0	0.18	0.14	0.12	0.13	0.19
		4	10.49	6.08	6.11	12.30	16.14
		8	24.37	14.12	14.22		

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative.

[00140] Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The

amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, at room temperature ($19\text{-}23^{\circ}\text{C}$) and at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations						
Powder Formulation (grams)						
Component	D1	D2	D3	D4	D5	D6
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

[00141] The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)								
Storage			Formulation					
	°C	Weeks	D1	D2	D3	D4	D5	D6
Liquid Formulations								
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		
	40	0	0.03	0.02	0.03	0.03	0.13	0.14

4	4.76	4.42	4.76	6.45	5.55	5.24
8	8.95	8.64	9.61	12.94	12.73	12.18
12	11.01	10.64	11.41	16.16		
26	17.18	17.11	18.30	27.36		

Example E: Stability of Solution Formulations of Enalapril Maleate.

[00142] Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5 °C ± 3 °C, at room temperature (19-23 °C) and at 40 °C ± 2 °C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

[00143] The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)								
Storage			Formulation					
	°C	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04

		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
	19-23	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28
		12	0.58	0.59	0.53	0.51	0.48	0.45
		26	1.10	1.10	1.00	0.95	0.97	0.92
		52					2.30	2.15
		62	3.02	3.04	2.75	2.64		
	40	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76	1.68
		8	4.02	3.99	3.99	3.62	3.37	3.13
		12	6.72	6.42	6.47	6.00	5.53	5.29
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		
	19-23	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.65	0.65	0.68	0.70	0.50	0.46
		8	1.17	1.19	1.20	1.23	1.03	0.95
		12	1.67	1.69	1.72	1.80	1.30	1.21
		26	3.36	3.38	3.42	3.57	3.07	2.90
		52					6.32	5.88
		62	7.99	8.02	8.04	8.57		
	40	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	4.85	4.93	5.19	5.42	3.33	3.25
		8	8.08	8.06	8.56	9.01	6.65	6.35
		12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5 °C and 19-23 °C.

[00144] The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in Figure 1 (5°C ± 3 °C) and Figure 2 (19-23 °C storage). These formulations all contained 20mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

[00145] Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10mg Enalapril Maleate Oral Solution vs. 10mg Epaned[®] Powder for Oral Solution (Reconstituted) Under Fasted Conditions

[00146] The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned[®] (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

[00147] Study design: Thirty-two healthy adult subjects received a single 10mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

[00148] During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

[00149] Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix[™] WinNonlin[®] (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

[00150] Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned

Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_{\max} were approximately 115% and 109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{\max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{\text{last}})$ and $\ln(AUC_{\text{inf}})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

[00151] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	10/31/2018	Gerold L. Mosher	43060-707.304	3572
21971	7590	12/14/2018	EXAMINER	
WILSON, SONSINI, GOODRICH & ROSATI			SPRINGER, STEPHANIE K	
650 PAGE MILL ROAD			ART UNIT	PAPER NUMBER
PALO ALTO, CA 94304-1050			1629	
			NOTIFICATION DATE	DELIVERY MODE
			12/14/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

<i>Decision Granting Request for Prioritized Examination (Track I)</i>	Application No. 16/177,159	Applicant(s) Mosher et al.	
	Examiner BRIAN W BROWN	Art Unit OPET	AIA (First Inventor to File) Status Yes

1. THE REQUEST FILED 31 October 2018 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).

B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to BRIAN BROWN at (571)272-5338. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/BRIAN W BROWN/ Petitions Examiner, OPET	
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patentdocket@wsgr.com

Office Action Summary**Application No.**

16/177,159

Applicant(s)

Mosher et al.

Examiner

STEPHANIE K SPRINGER

Art Unit

1629

AIA Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 31 October 2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a) ☐ This action is **FINAL**.

2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) ____ is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1-30 is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date ____.

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: ____.

Paper No(s)/Mail Date ____.

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DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Status

This application is a continuation of application 16/003,994, now US Patent 10,154,987, filed on June 8, 2018, which is a continuation of application 15/802,341, now US Patent 10,039,745, filed on November 2, 2017, which is a continuation of application 15/613,622, now US Patent 9,808,442, filed on June 5, 2017, which is a continuation of application 15/081,603, now US Patent 9,669,008, filed on March 25, 2016 and claims priority to US provisional application 62/310,198, filed on March 18, 2016.

This application was granted Track One status on December 14, 2018.

Claims 1-30 are pending and are the subject of the Office Action below.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 14-27, and 29-30 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

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Claims 1, 17, 18, and all claims dependent therefrom, are indefinite for failing to clearly and precisely set forth the nature of the preservative meeting the claimed requirements, and distinguishing the components of the buffer from the preservative. Claims 1, 17, and 18 are generally drawn to a stable oral liquid formulation, comprising or consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising citric acid and sodium citrate;

(iii) a preservative; and

(iv) water.

The Examiner notes that the claimed compositions are required to comprise citric acid and sodium citrate as a buffer. Regarding the preservative, dependent claims 12 and 27 recite particular preservatives meeting the limitations, including citric acid. It is unclear if a single amount of citric acid in the composition would meet the requirements of both the preservative and the buffer, as the buffer itself comprises citric acid. Absent this information, the claim clearly fails to set forth the metes and bounds of the subject matter for which Applicant is presently seeking protection.

The Examiner notes that claim 14 further limits claim 12, reciting "The stable oral liquid formulation of claim 12, wherein the sodium benzoate is about 0.2 to about 1.2 mg/ml"; however, there is no express requirement that the preservative is specifically sodium benzoate in a concentration of about 0.2 to about 1.2 mg/ml. The Examiner suggests amending claim 14 so as to clearly convey that the preservative is sodium benzoate in the recited amount, *i.e.*, "The stable oral liquid formulation of claim 12, wherein the preservative is sodium benzoate, wherein the sodium benzoate is about 0.2 to about 1.2 mg/ml".

For these reasons, the metes and bounds of the present claims cannot be determined and one having ordinary skill in the art would not necessarily be reasonably apprised of the scope of

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 Art Unit: 1629

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the claims. In light of such, claims 1-12, 14-27, and 29-30 fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are thus properly rejected.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 4-13, 14-19, 21-27, 29, and 30 are rejected under 35 U.S.C. 102(a)(1) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Nahata et al., "Stability of elanapril maleate in three extemporaneously prepared oral liquids", *Am. J. Health-Syst. Pharm.*, 1998, vol. 55, pages 1155-1157 (cited in PTO-892).

Claims 1, 2, 4-13, 14-19, 21-27, 29, and 30 are generally drawn to compositions comprising:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising citric acid and sodium citrate;

(iii) a preservative; and

(iv) water.

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Nahata teaches formulations comprising

- (i) 1 mg/ml enalapril;
- (ii) a buffer comprising citric acid and sodium citrate; and
- (iv) water.

In particular, Nahata teaches preparation of an aqueous solution comprising 1 mg/ml enalapril in a citrate buffer solution (page 1156, column 1, paragraph 2). The citrate buffer solution is prepared accordingly: "Prepare the isotonic citrate buffer solution (pH 5.0) by dissolving 0.353 g of Citric Acid Monohydrate Granular, USP, 1.01 g of Sodium Citrate Dihydrate Granular, USP, and 0.54 g of sodium chloride in 100 mL of distilled water" (page 1157, Appendix and footnote a).

As noted in the rejection *supra*, claim 12 recites the use of citric acid as a preservative. The ordinarily skilled artisan would thus recognize the buffer solution taught by Nahata to fulfill the requirements of both the buffer and the preservative. In other words, citric acid serves as both a component of the buffer system, as well as a preservative.

Regardless, Nahata also teaches the use of another component meeting the requirements of a preservative. The ordinarily skilled artisan would recognize the sodium chloride in the citrate buffer solution taught by Nahata to meet the instant requirements of a preservative; see Parish, "How do salt and sugar prevent microbial spoilage?", *Scientific American*, 2006 (cited in PTO-892; cited to show a fact). Although the instant claims and specification do not explicitly recite sodium chloride as a preservative, regarding the preservative, the specification recites, "Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility" (paragraph 44). The specification further recites examples of preservatives; however, the Examiner notes that these are merely exemplary, and non-limiting. Accordingly, the formulation taught by Nahata anticipates the formulation of claims 1, 5, 12, 15, and 17.

Additionally, the claimed composition would have been *prima facie* obvious to one having ordinary skill in the art in view of the teachings of Nahata. In addition to the formulation comprising

- (i) 1 mg/ml enalapril;

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- (ii) a buffer comprising citric acid and sodium citrate;
- (iii) a preservative, such as sodium chloride or citric acid; and
- (iv) water,

Nahata also teaches an aqueous solution comprising 1 mg/ml enalapril in a mixture of Ora-Sweet and Ora-Plus (page 1156, column 1, paragraph 2). Ora-Sweet and Ora-Plus are commercially available from Paddock Laboratories (page 1157, footnotes d and e). Ora-Sweet is an aqueous solution comprising sucrose, glycerin, sorbitol, flavoring, citric acid, sodium phosphate, methylparaben, and potassium sorbate; Ora-Plus is an aqueous solution comprising microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, flavoring, citric acid, sodium phosphate, simethicone, methylparaben, and potassium sorbate; both Ora-Sweet and Ora-Plus have a pH of 4.2. Thus, the formulation taught by Nahata comprising 1 mg/ml enalapril in a mixture of Ora-Sweet and Ora-Plus comprises

- (i) 1 mg/ml enalapril;
- (ii) citric acid;
- (iii) a preservative, such as citric acid, methylparaben, potassium sorbate; and
- (iv) water.

The formulations comprising Ora-Sweet and Ora-Plus also comprise sweeteners and flavoring agents, while not containing mannitol or silicon dioxide, thereby meeting the requirements of claims 2, 4-6, 19, and 21-23.

Accordingly, one having ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in arriving at the instantly claimed composition in view of the teachings of Nahata. Nahata teaches aqueous compositions comprising

- (i) 1 mg/ml enalapril;
- (ii) citric acid and sodium citrate;
- (iii) a preservative, such as citric acid, methylparaben, potassium sorbate; and
- (iv) water.

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It would be within the purview of the ordinarily skilled artisan to arrive at a formulation having the desired properties in view of the teachings of Nahata. For example, Nahata teaches the superiority of the citrate buffer formulation and the Ora-Sweet/Ora-Plus formulations; the ordinarily skilled artisan would optimize the combination of the diluents in order to achieve a formulation having improved properties. In other words, one would recognize the flavorings, sweeteners, and preservatives of the Ora-Sweet/Ora-Plus formulation to be beneficial in combination with the buffer comprising both citric acid and sodium citrate. Absent evidence of criticality in the selection of a particular preservative or particular amounts of each of the components, optimizing the formulations taught by Nahata would fall within routine optimization for the ordinarily skilled artisan. The Examiner notes that instant claims 1, 17, and 18 broadly encompass compositions comprising a wide range of amounts of components, leaving ample room for optimization of the formulation taught by Nahata.

Regarding the limitations directed towards the pH of the formulation, as recited in claims 9-11 and 24-26, Nahata teaches a citrate buffer having a pH of 5, and an Ora-Sweet/Ora-Plus mixture having a pH of 4.2. The composition of Nahata fulfills the instant requirement of a pH of “about 3.5” as a composition having a pH of 4.2 would reasonably be considered to be “about 3.5” absent an explicit definition provided by Applicant as to the amount of variation tolerated by the term “about” as used in the instant claims. The use of the word “about” in a claim is appropriate where the claim contains a range of components with no absolute boundaries, and is only limited to the extent that prior art exists which would limit broad interpretation of the claim. See *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1217-1218, 18 USPQ2d 1016 (Fed. Cir. 1991).

Although Nahata does not explicitly teach that the formulation is stable at about 5 ± 3 °C for at least 12 months, or that the formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period, the composition taught by Nahata is identical to that instantly claimed. Any properties exhibited by or benefits provided the composition are inherent and are not given

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patentable weight over the prior art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

In re Best (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe necessarily includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation, the burden is shifted to the Applicants to "prove that the subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 592, second column, first full paragraph). There is no requirement that a person having ordinary skill in the art would have recognized this necessarily present disclosure at the time of the invention, but only that the subject matter is, in fact, necessarily present in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). In the instant case, the prior art formulation contains the same active ingredient and excipients as that presently claimed in the same physical formulation and in the same amounts, and, therefore, the resultant property of stability at about 5 ± 3 °C for at least 12 months, or that the formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period, must necessarily be present in the prior art composition, absent factual evidence to the contrary. The burden is now shifted to Applicant to prove that, in fact, the prior art formulation does not possess these same claimed characteristics.

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Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and

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approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,669,008, herein referred to as '008. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-20 of '008 are generally drawn towards stable oral liquid formulations comprising enalapril, a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Claim 18 is drawn to a particular species of composition, namely, a stable oral liquid formulation, consisting essentially of: (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml sodium benzoate; (v) a flavoring agent; (vi) water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-20 of '008 are drawn to a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-20 of '008.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '008.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 9,808,442, herein referred to as '442. Although the claims at issue are not identical, they are not patentably distinct from each other.

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Claims 1-30 of '442 are generally drawn towards methods of treating hypertension, heart failure, and left ventricular dysfunction in a subject, comprising administering a stable oral liquid formulation comprising enalapril; a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-30 of '442 are drawn to methods of use of a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-30 of '442.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '442.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 10,039,745, herein referred to as '745. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-20 of '745 are generally drawn towards stable oral liquid formulations comprising enalapril, a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-20 of '745 are generally drawn towards a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-20 of '745.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '745.

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Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 10,154,987, herein referred to as '987. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-30 of '987 are generally drawn towards methods of treating hypertension, heart failure, and left ventricular dysfunction in a subject, comprising administering a stable oral liquid formulation comprising enalapril; a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-30 of '987 are drawn to a method of using a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-30 of '987.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '987.

Conclusion

No claims are allowed in this application.

If applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported *in ipsius verbis*, clarification on the record may be helpful). Should applicants present new claims, applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JEFFREY S LUNDGREN whose telephone number is (571)272-5541. The examiner can normally be reached on Monday through Thursday from 8 am to 5 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren, can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-270-8380.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stephanie Springer/
Examiner, Art Unit 1629

/JEFFREY S LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

Electronically Filed: March 1, 2019

Attorney Docket No.: 43060-707.304

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

First Named Inventor	: Gerold L. MOSHER	Confirmation No.:	3572
U.S. Application No.	: 16/177,159		
Filed	: October 31, 2018	Customer No.:	021971
TC/A.U.	: 1629		
Examiner	: SPRINGER, STEPHANIE K		
Title	: ENALAPRIL FORMULATIONS		

RESPONSE TO THE NON-FINAL OFFICE ACTION DATED JANUARY 25, 2019

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant hereby submits a response to the Office Action dated January 25, 2019 (the “Office Action”), in the above-identified application. Applicant respectfully requests amendment of the patent application, and reconsideration and allowance of the pending claims. The Commissioner is hereby authorized to charge any fees associated with the filing of this response to Deposit Account No. 23-2415, referencing Docket No. 43060-707.304.

Amendments to the Claims, reflecting the status of the claims, begin on page **2**.

Remarks begin on page **6**.

The **Conclusion** is on page **14**.

Amendments to the Claims

This listing of claims will replace all prior versions, amendments and listings of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicant reserves the right to pursue the subject matter of the withdrawn claims in this or any other appropriate patent application.

Listing of the Claims:

1. (Currently Amended) A stable oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising citric acid and sodium citrate;
 - (iii) a preservative, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and
 - (iv) water;

wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
2. (Previously Presented) The stable oral liquid formulation of claim 1 further comprising a sweetener.
3. (Previously Presented) The stable oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. (Previously Presented) The stable oral liquid formulation of claim 1 further comprising a flavoring agent.

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5. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
6. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
7. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the buffer comprises about 0.8 to about 3.5 mg/ml citric acid.
8. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the buffer comprises about 0.1 to about 0.8 mg/ml sodium citrate.
9. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is less than about 3.5.
10. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.
11. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is about 3.3.
12. (Canceled)
13. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the preservative is sodium benzoate.
14. (Currently Amended) The stable oral liquid formulation of claim [[12]]1, wherein the preservative is sodium benzoate, and wherein the sodium benzoate is about 0.2 to about 1.2 mg/ml.
15. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 18 months.
16. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 24 months.
17. (Currently Amended) A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising citric acid and sodium citrate;

(iii) a preservative, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

18. (Currently Amended) A stable oral liquid formulation, comprising:

(i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate;

(iii) about 1% to about 30% (w/w of solids) of a preservative, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

19. (Previously Presented) The stable oral liquid formulation of claim 18 further comprising a sweetener.

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20. (Previously Presented) The stable oral liquid formulation of claim 19, wherein the sweetener is sucralose.
21. (Previously Presented) The stable oral liquid formulation of claim 18 further comprising a flavoring agent.
22. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the formulation does not contain mannitol.
23. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the formulation does not contain silicon dioxide.
24. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the pH of the stable oral liquid formulation is less than about 3.5.
25. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.
26. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the pH of the stable oral liquid formulation is about 3.3.
27. (Canceled)
28. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the preservative is sodium benzoate.
29. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 18 months.
30. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 24 months.

Electronically Filed: March 1, 2019

Attorney Docket No.: 43060-707.304

REMARKS

Claims 1-11, 13-26, and 28-30 are pending in this application. By way of this response, claims 1, 14, 17, and 18 have been amended, and claims 12 and 27 have been canceled. No new matter is presented by way of the amendments.

Withdrawal of any subject matter herein does not constitute an admission that the subject matter is unpatentable for any reason and Applicant reserves the right to file claims directed to withdrawn subject matter in this or a related application.

Rejection Under 35 U.S.C. §112(b)

Claims 1-12, 14-27, and 29-30 are rejected under 35 U.S.C. § 112(b) as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Without acquiescing to the Office's rejection but solely in an effort to expedite prosecution, claims 1, 17, and 18 have been amended to recite "wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin." Claims 12 and 27 are canceled.

As such, the § 112(b) rejections are now moot. Accordingly, Applicant respectfully requests the rejections be withdrawn.

Rejection Under 35 U.S.C. §102/103

Claims 1, 2, 4-13, 14-19, 21-27, 29, and 30 are rejected under 35 U.S.C. 102(a)(1) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Nahata et al., "Stability of elanapril maleate in three extemporaneously prepared oral liquids", *Am. J. Health-Syst. Pharm.*, 1998, vol. 55, pages 1155-1157 ("Nahata").

The Office alleges that "the formulation taught by Nahata anticipates the formulation of claims 1, 5, 12, 15, and 17." Specifically, the Office states that "Nahata teaches preparation of an aqueous solution comprising 1 mg/ml enalapril in a citrate buffer solution" and an "ordinary skilled artisan would recognize the sodium chloride in the citrate buffer solution taught by Nahata to meet the instant requirements of a preservative."

Further, the Office alleges that “the formulations [taught in Nahata] comprising Ora-Sweet and Ora-Plus also comprise sweeteners and flavoring agents . . . thereby meeting the requirements of claims 2, 4-6, 19, and 21-23.”

In making the rejections, the Office does not dispute that “Nahata does not explicitly teach that the formulation is stable at about 5 ± 3 °C for at least 12 months, or that the formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.” Nevertheless, the Office takes the position that “[a]ny properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art.”

With respect to the obviousness rejections, the Office states that “Nahata teaches aqueous compositions comprising (i) 1 mg/ml enalapril; (ii) citric acid and sodium citrate; (iii) a preservative, such as citric acid, methylparaben, potassium sorbate; and (iv) water,” and the Office alleges that “[i]t would be within the purview of the ordinarily skilled artisan to arrive at a formulation having the desired properties in view of the teachings of Nahata.”

Applicant respectfully disagrees.

Applicant respectfully submits that Nahata does not teach or suggest all the elements of the claimed formulations, e.g., the stability element—“the formulation is stable at 5 ± 3 °C for at least 12 months”—is not disclosed either expressly or inherently. And such a superior stability is an unexpected result. Applicant further submits an Inventor Declaration by Dr. Gerold Mosher dated February 2, 2017 (“the Mosher Declaration”), with evidence to overcome the §102/103 rejections asserted by the Office, as discussed in greater detail below.

A. The §102 Rejection

a. The Cited Reference Does Not Teach Enalapril Oral Liquid Formulations That Are Stable at 5 ± 3 °C For At Least 12 Months

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“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

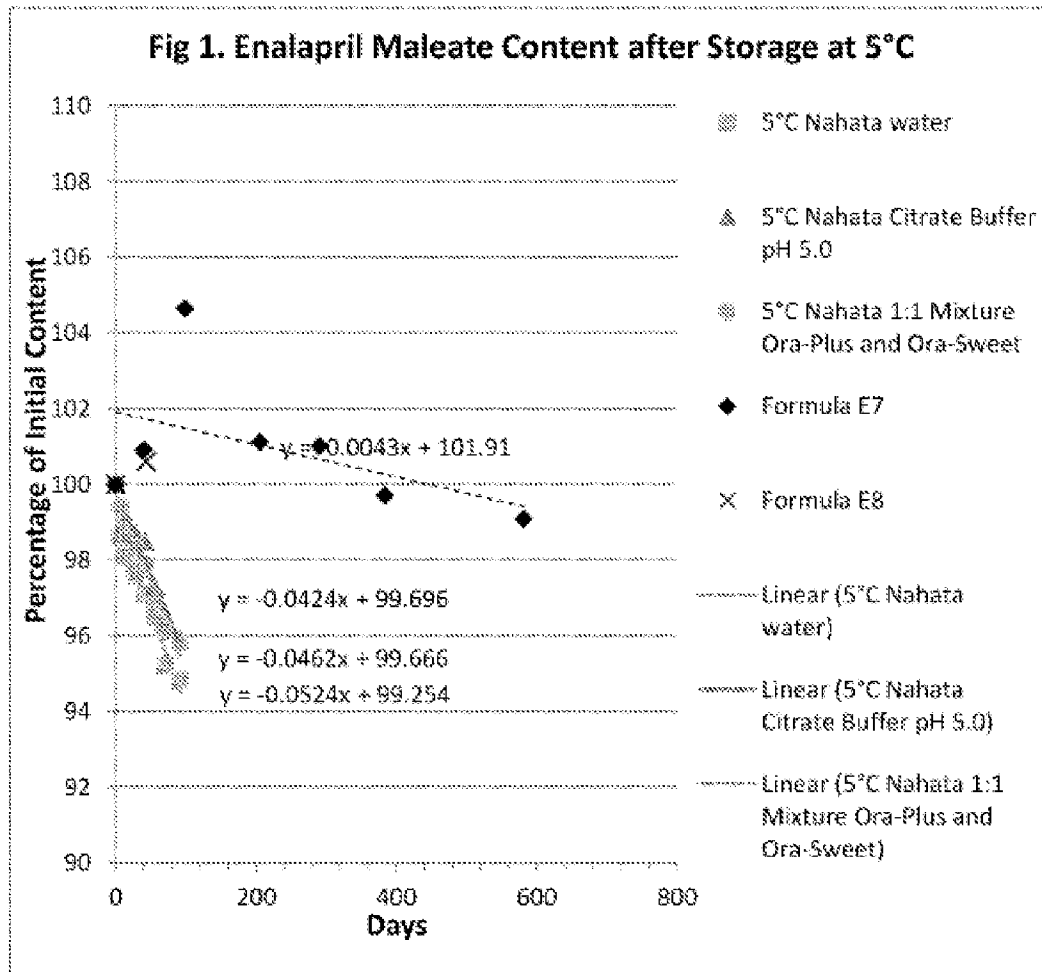
Nahata does not disclose enalapril oral liquid formulations that are stable at 5 ± 3 °C for at least 12 Months, which is one of the elements in the present claims.

Specifically, claim 1 is directed to a stable oral liquid formulation comprising (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer comprising citric acid and sodium citrate; (iii) a preservative, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and (iv) water; **wherein the formulation is stable at about 5 ± 3 ° C for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.** Claim 17 and claim 18 similarly recite a formulation in a “consisting essentially of” format and in a “% w/w” format, respectively.

The Specification and Drawings of the instant application provide support and evidence of this stability; for example, Table E-2 depicts very little amounts of diketopiperazine or enalaprilat degradants formed in formulations E1 to E6 when stored at 5 °C. Table E-1 shows that formulations E1 to E6 contain enalapril, citric acid, sodium citrate, a preservative, and water, which Applicant notes are the claimed components of the instant applications.

Moreover, the Mosher Declaration provides additional data supporting the claimed stability by comparing the dramatic differences in stability between the enalapril oral liquid formulations of the present application with the stability of the enalapril liquid preparation in Nahata. In the Mosher Declaration, Dr. Mosher plotted graphically with linear regression of the data for extrapolation of the available refrigerated (5 °C) and room temperature (25 °C) stability data published by Nahata as well as E7 and E8 enalapril formulations, which are exemplary

formulations of the present application. The stability comparisons at 5 °C are presented in Fig 1. as below:



As Dr. Mosher explains, “Table A and Fig. 1 show that E7 exhibits excellent stability for at least 18 months (581 days) at 5 °C with essentially no loss of enalapril content in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at 5 °C for more than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.” Mosher Declaration, ¶21. Evidently, a stability of at least 12 months at 5 ± 3 °C is not an inherent property of the Nahata formulations.

Further, Applicant respectfully points out that the instant application is directed to novel stable enalapril oral liquid formulations with superior stability and uniformity properties. As Dr. Mosher explains, the “currently approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in “Nahata” and subsequently administering the suspension to the patient, or (3) reconstituting a powder in a liquid carrier” and “[f]or the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination.” Mosher Declaration, ¶¶10-11. The stable enalapril oral liquid formulations in the present application represent an elegant solution over the previous methods of obtaining liquid enalapril formulation.

Thus, the data presented in the Mosher Declaration clearly demonstrates that the extemporaneous preparations of Nahata do not meet the stability requirement of the present claims.

As such, Nahata does not disclose any liquid formulations of enalapril having a stability **at about 5 ± 3 °C for at least 12 months**, either explicitly or by inherency. Accordingly, Applicant respectfully requests the §102 rejections be withdrawn.

B. The §103 Rejection

a. The Cited Reference Provides No Reasonable Expectation of Success of the Claimed Subject Matter

Obviousness does not require absolute predictability, however, at least some degree of predictability is required. MPEP § 2143.02. To have a reasonable expectation of success, one must be motivated to do more than merely “vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *Medichem, S.A. v. Robaldo*, 327 F.3d 1157, 1165 (Fed. Cir. 2006).

There is no expectation from Nahata that the extemporaneously prepared oral liquid formulation can be modified to have a stability at about 5 ± 3 °C for at least 12 months (365 days). In fact, as Dr. Mosher explains, “the extrapolated lines [in Nahata] show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.” Mosher Declaration, ¶12. Thus, one of ordinary skill in the art would not reasonably expect, based on the teachings in Nahata, to make a formulation having a stability at about 5 ± 3 °C for a period of time that is more than three times longer than the Nahata formulation.

Thus, the Office has not established how one of skill in the art would expect to modify the extemporaneously prepared formulation in Nahata and to arrive at a stable oral liquid formation meeting all the elements of the present claims.

Further, the enalapril tablets used in the extemporaneous preparations of Nahata contain, in addition to enalapril, lactose, magnesium stearate, sodium bicarbonate, starch, and iron oxide. Ora-Plus is an oral suspending vehicle that has a pH of approximately 4.2 and that contains purified water, microcrystalline cellulose, sodium carboxymethylcellulose, xanthan gum, carrageenan, buffering agents (trisodium phosphate and citric acid), an antifoaming agent (simethicone), and preservatives (potassium sorbate and methylparaben). Ora-Sweet syrup vehicle is a flavoring vehicle that is buffered to a pH of approximately 4.2 and that contains purified water, sucrose, glycerin, sorbitol (5%), flavoring, buffering agents (sodium phosphate and citric acid), and preservatives (potassium sorbate and methylparaben). Nahata therefore teaches that these extemporaneously prepared suspensions from enalapril tablets contain a myriad of components, the majority of which are not present in the presently claimed formulations. The following table lists the components that are present in the Nahata formulation:

Enalapril Extemporaneous Formulation (Ora-Sweet/Ora-Plus)
Enalapril
Lactose
magnesium stearate
sodium bicarbonate

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Starch
iron oxide
microcrystalline cellulose
carboxymethylcellulose
xanthan gum
carrageenan
calcium sulphate
trisodium phosphate
citric acid
dimethicone
potassium sorbate
methylparaben
Flavoring
Sorbitol
Glycerin
sucrose
Water

Apparently, the extemporaneously prepared formulation in Nahata contains 19 components in addition to enalapril and water. As such, Nahata does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations, which can extend the stability from less than 100 days to at least 12 months at 5 °C. One of skill in the art would need to consider all of these excipients and, through trial-and-error, determine whether each and every one of these components is necessary for stability or if they could be varied or eliminated.

Thus, the Office has not demonstrated a reasonable expectation of success based on Nahata.

b. Unexpected Results

Applicant submits that the subject matter in the claims has unexpected results with respect to stability of liquid enalapril formulations.

As explained in the Mosher Declaration, the claimed stable enalapril liquid formulations are dramatically much more stable than the extemporaneous enalapril preparations of Nahata. In the Mosher Declaration, Dr. Mosher plotted graphically, with linear regression of the data for

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extrapolation of the stability data published in Nahata, as well as corresponding E7 and E8 enalapril formulations, which are exemplary formulations of the present claims. *See*, Mosher Declaration, Fig 1 and Fig 2.

As evidenced by the graphs, the E7 formulation demonstrates no loss of enalapril for at least 12 months at 5 °C and about 100 days at 25 °C. The E8 formulation, which has only one data point, is expected to trend similarly. These results drastically contrast with the stability or lack thereof in the extemporaneous and reconstituted enalapril preparations where in these cases, the enalapril degrades substantially after initial preparation. At about 90-100 days, the extemporaneous preparations are at about 95% of the starting enalapril concentration when stored at either 4 °C or 25 °C.

The unexpected stability results of the E7 and E8 formulations are not taught by, and could not have been predicted or contemplated by Nahata.

Accordingly, Applicant respectfully requests the §103 rejection be withdrawn.

Double Patenting Objection

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,669,008, claims 1-30 of U.S. Patent No. 9,808,442, claims 1-20 of U.S. Patent No. 10,039,745, and claims 1-30 of U.S. Patent No. 10,154,987.

Without acquiescing in this ground of rejection and solely in an effort to expedite prosecution, Applicant hereby submits Terminal Disclaimers with respect to U.S. Patent No. 9,669,008, U.S. Patent No. 9,808,442, U.S. Patent No. 10,039,745, and U.S. Patent No. 10,154,987.

The Terminal Disclaimers obviate the present rejections. Accordingly, Applicant respectfully requests that the rejections be withdrawn.

In view of the remarks and amendments submitted herein, Applicant believes that the Application is in condition for allowance and such action is earnestly solicited.

* * *

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CONCLUSION

Applicant submits that this response fully addresses the Office Action mailed on January 25, 2019. Applicant believes that for the reasons set forth herein the pending claims are in condition for allowance and early and favorable consideration is respectfully requested.

Should the Examiner have any questions or concerns, the Examiner is encouraged to contact the undersigned attorney at (617) 598-7823.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: March 1, 2019

By: /Clark Lin/
Clark Y. Lin, Ph.D., Esq.
Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2306
Customer No. 021971

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Examiner: Stephanie K. Springer
Serial No.: 15/081,603	Confirmation No.: 3892
Filed: March 25, 2016	Customer No.: 021971
Title: ENALAPRIL FORMULATIONS	

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132

I, **Gerold Mosher**, do hereby declare as follows:

1. I am currently employed at Silvergate Pharmaceuticals, Inc.
2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.
3. I have been employed at Silvergate Pharmaceuticals since 2013, as Vice President of Drug Development. As part of my job duties, I develop oral solutions for pediatric use. I have a small laboratory where I develop, characterize and move formulations through the steps required for FDA approval and eventual sale.
4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also

been employed by small startup companies to develop new solubilizing technology for oral, injectable and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for almost 38 years, and have extensive experience in developing pharmaceutical formulations. My Curriculum Vitae is attached as Exhibit A.

6. I am familiar with the subject matter claimed in patent application 15/081,603, and am a named inventor on this application. Silvergate Pharmaceuticals is also the Assignee of the '603 application.

7. I am aware of the Non-Final Office Action mailed in this matter on January 17, 2017. I am also aware that the oral enalapril liquid formulation claims stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over US 8,568,747, Nahata et al. (Stability of Enalapril Maleate in three Extemporaneously Prepared Oral Liquids) ("Nahata"), Product Information of Bicitra (Sodium Citrate and Citric Acid Oral Solution) ("Bicitra"), Product Information of Ora-Sweet ("Ora-sweet"), and Rippley et al. (Pharmacokinetics Assessment of an Oral Enalapril Suspension for Use in Children) ("Rippley"). I have reviewed these cited references in the Non-Final Office Action.

8. I am submitting this declaration to address the comments made in the Office Action.

9. The '603 application relates to enalapril oral liquid formulations that are stable for least 12 months at 5 ± 3 °C. The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water at a pH of less than 3.5. Development of this described enalapril formulation was oriented on preparing a safe, stable, soluble oral liquid with minimal degradation and having acceptable taste for pediatric patients.

10. The currently approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in "Nahata" and subsequently administering the suspension to the

patient, or (3) reconstituting a powder in a liquid carrier, such as the described enalapril powder in US 8,568,747.

11. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty in swallowing oral dosage forms. For the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination. Similarly, reconstituting powders into a liquid carrier also requires an extra step and could introduce variability, solubility and contamination issues during the reconstitution.

12. As compared to these currently available methods, the enalapril oral liquid formulations claimed in the '603 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

13. It should be appreciated that the oral enalapril liquid formulations of the present claims are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

14. Evidence of this stability is found in exemplary formulations E7 and E8 which show minimal degradation as compared to current formulations. In this study, exemplary formulations E7 and E8 were stored at either refrigerated condition (5 °C) or at ambient condition (25 °C). Formulations details for E7 and E8 are as follows:

Composition of Enalapril Maleate Formulations		
Component	E7	E8
Enalapril maleate	1.00	1.00
Citric acid anhydrous	1.80	1.82
Sodium citrate anhydrous	0.16	0.15
Sodium benzoate	1.00	1.00
Sucralose	0.70	0.70
Mixed berry flavor	0.50	0.50
Water	qs	qs
pH (measured)	3.3	3.3

qs = sufficient quantity

15. In my review of the references cited in the Office Action, none of the references describe this stability of at least 12 months at 5 ± 3 °C or any means of achieving this stability for enalapril formulations.

16. I have reviewed Nahata which describes the extemporaneous preparation of oral liquid enalapril formulations by crushing enalapril tablets with a mortar and pestle and suspending the resulting ground tablets in water, citrate buffer, or Ora-Plus/Ora-Sweet. On stability, Nahata states that the “compounded oral liquids [were] stable for 91 days at 4 and 25 °C” defining stable as “concentration after storage was $\geq 90\%$ of the initial concentration. Table 1 of Nahata shows that the enalapril extemporaneous formulations exhibited about 5% loss of enalapril after about 56 days at 4 °C and about 5% loss of enalapril after about 91 days at 25 °C.

17. I have also reviewed US 8,568,747 which describes an oral liquid enalapril formulation obtained by reconstituting an enalapril powder in a liquid. The table in example 6 of US 8,568,747 shows that the resulting oral liquid formulation exhibited about 5% loss of enalapril after about 8 weeks at 25 °C.

18. I additionally reviewed Bicitra, Ora-sweet, and Rippley and they do not provide any stability of enalapril formulations whatsoever.

19. To compare the stability of the enalapril extemporaneous preparations as described in Nahata and the reconstituted liquid formulation of US 8,568,747, I submit the following data which depicts the enalapril content of formulations E7 at 5 °C and 25 °C and E8 at 5 °C in Table A and Table B:

Table A: Enalapril content in formulations after storage at 5 °C¹

Days	Nahata			E7	E8
	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet		
0	100	100	100	100	100
7	98.6	98.7	99.4		
14	98.1	99.1	98.6		
28	97.6	98.7	98.4		
40				100.9	
42	97.1	98.5	97.9		100.3
56	96.5	97.3	96.9		
70	95.2	96.3	96.1		
91	94.8	95.9	95.8		
99				104.7	
205				101.1	
290				101.0	
383				99.7	
581				99.1	

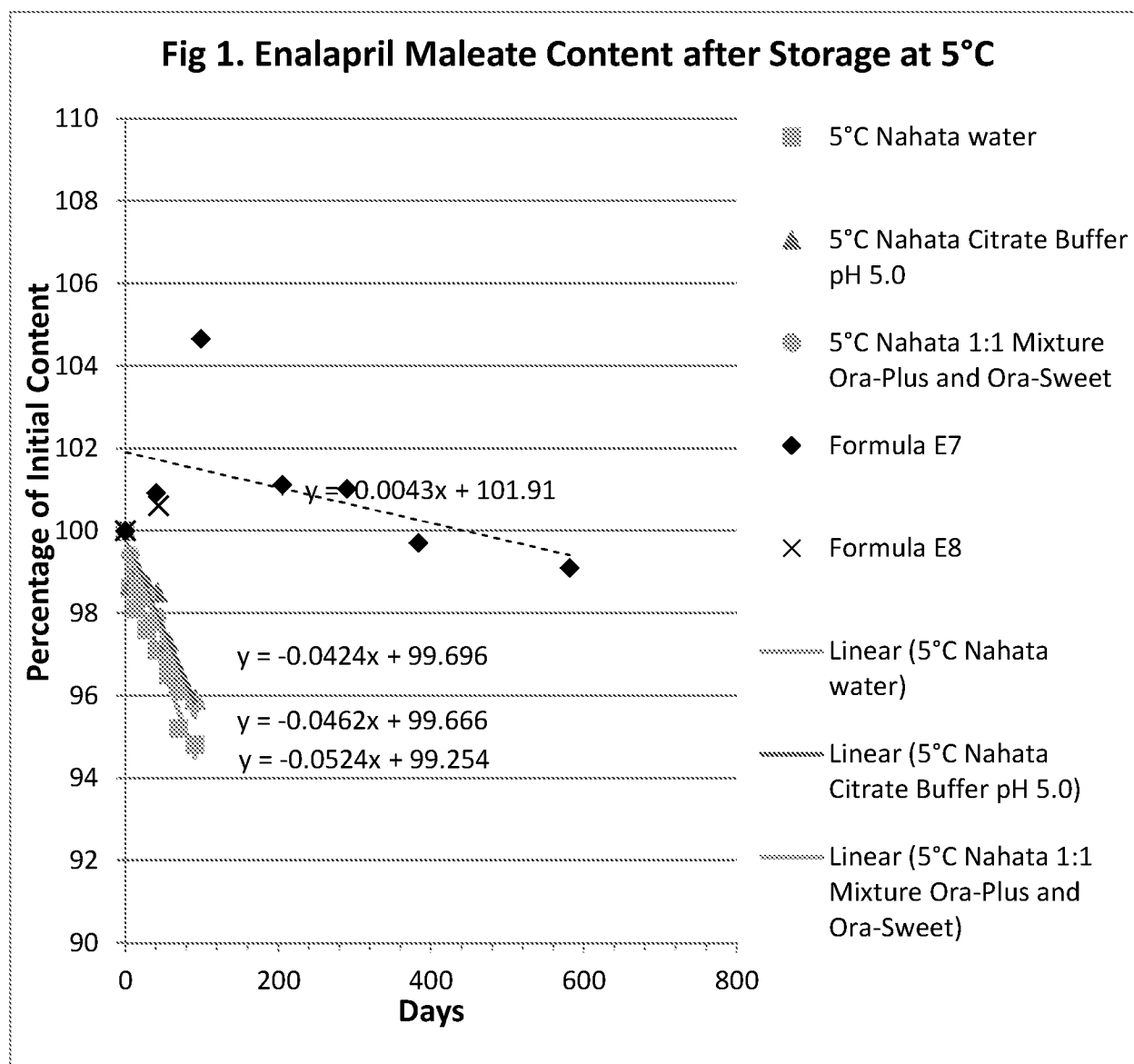
Table B: Enalapril content in formulations after storage at 25 °C

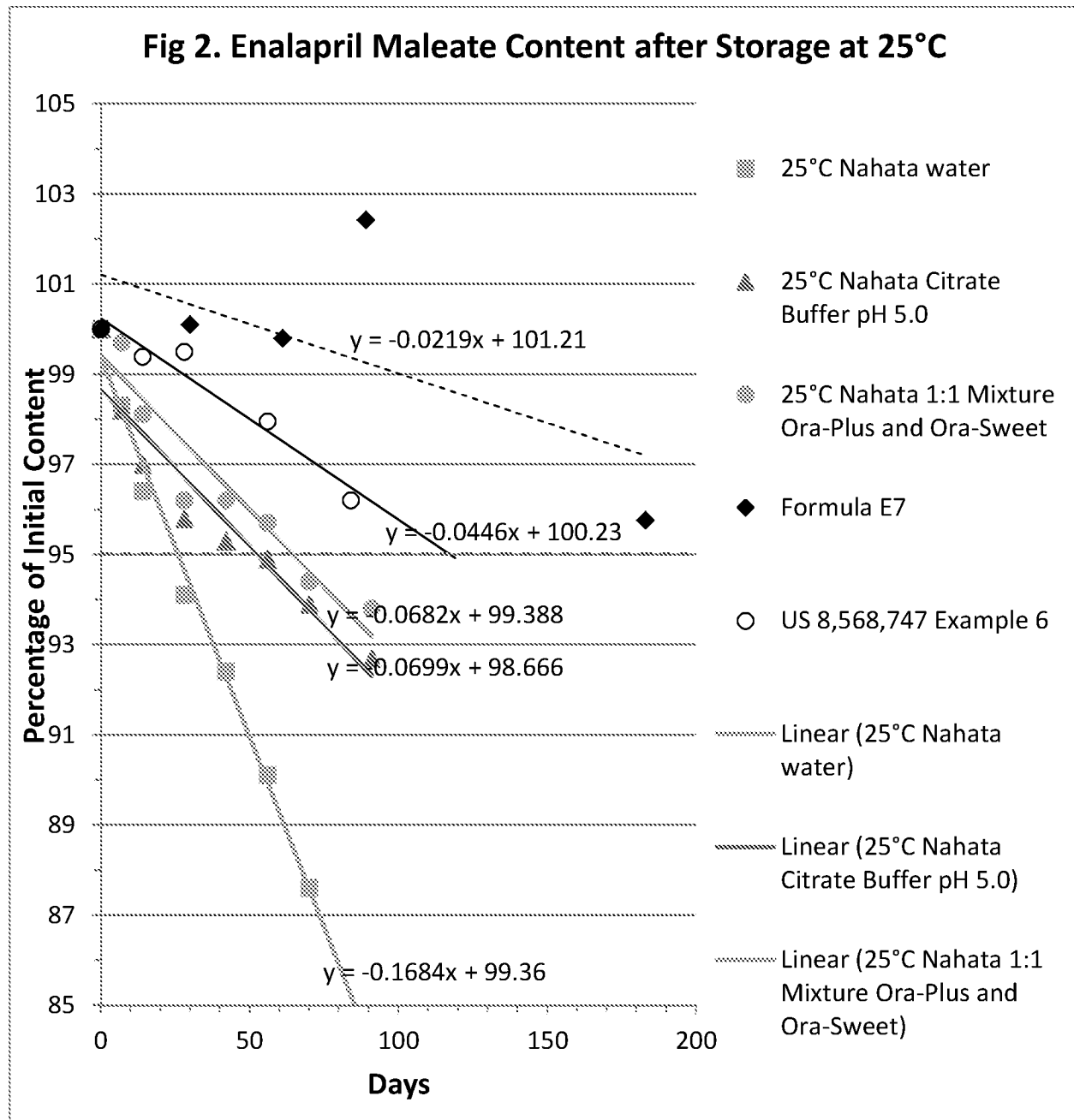
Days	Nahata			US 8,568,747	E7
	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	Example 6	
0	100	100	100	100	100
7	98.3	98.2	99.7		
14	96.4	97	98.1	99.4	
28	94.1	95.8	96.2	99.5	
30					100.1
42	92.4	95.3	96.2		
56	90.1	94.9	95.7	97.9	
61					99.8

¹ I note that US 8,568,747 does not provide stability data of the reconstituted liquid formulation at 5 °C.

70	87.6	93.9	94.4		
84				96.2	
89					102.4
91	84.1	92.7	93.8		
183					95.8

20. To further describe the contrast in stability, the enalapril concentrations published by Nahata, the US 8,568,747 enalapril concentrations, and the concentrations from E7 and E8 are plotted graphically (Fig. 1: 5 °C and Fig. 2: 25 °C) with linear regression of the data for extrapolation.





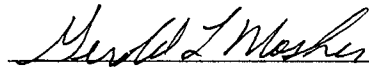
21. Table A and Fig. 1 show that E7 exhibits excellent stability for at least 18 months (581 days) at 5 °C with essentially no loss of enalapril content in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at 5 °C for more than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.

22. Table B and Fig. 2 show that E7 also exhibits better stability for at least 6 months (183 days) at 25 °C in contrast to the Nahata preparations and the reconstituted formulation of US 8,568,747.

23. The additional enalapril content data submitted for E7 and E8 shows that the formulations of the present application are significantly more stable, which in my opinion reflects the superior results and advantages, obtained with the oral liquid enalapril formulation of the present claims.

24. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under 18 U.S.C. 1001.

Respectfully submitted on this 2nd day of February, 2017

A handwritten signature in cursive script, appearing to read "Gerold L. Mosher", is written over a horizontal line.

Gerold L. Mosher, Ph.D.

ADDRESSES

Silvergate Pharmaceuticals, Inc.
 7300 West 110th Street, Suite 950
 Overland Park, KS 66210
 (913) 424-9294
 Jerry.mosher@silvergatepharma.com

Home
 12215 Avila Drive
 Kansas City, MO 64145
 Mobile (913) 424-9294
 jerry@coweemosher.com

EDUCATION

Ph.D., Pharmaceutical Chemistry (1986) University of Kansas, Lawrence, KS
 MS, Pharmaceutical Chemistry (1984) University of Kansas, Lawrence, KS
 BS, Pharmacy (1979) University of Kansas, Lawrence, KS

PROFESSIONAL EXPERIENCE

SILVERGATE PHARMACEUTICALS, INC (2013-Present)

Vice President of Drug Development

VERROW PHARMACEUTICALS, INC., Lenexa, KS (2008-present)

Scientific Advisor (2013-present)

Chief Scientific Officer and Vice President of Product Development (2008-2013)

CYDEX PHARMACEUTICALS, INC., Overland Park, KS (1998-2008)

Sr. Director, Product Development

UNIVERSITY OF MISSOURI-KANSAS CITY, Kansas City, MO (1996-1998)

Research Associate Professor, Division of Pharmaceutical Science (1996-1998)

Associate Director of the Center for Pharmaceutical Technology (1996-1998)

MIDWEST RESEARCH INSTITUTE, Kansas City, MO (1995-1996)

Manager, Pharmaceutical Product Development Section (1996)

Senior Chemist, Formulations Group Leader (1995)

INTERx DIVISION OF MERCK & COMPANY, Lawrence, KS (1992-1995)

Research Fellow

ELI LILLY & COMPANY, Indianapolis, IN (1986-1992)

Research Scientist (1990-1992)

Senior Pharmaceutical Chemist (1986-1990)

ST. JOSEPH HOSPITAL, Concordia, Kansas (1979-1981)

Staff Pharmacist

MEMBERSHIPS

American Association of Pharmaceutical Scientists (AAPS)

Phi Lambda Upsilon Honorary Chemical Society

Sigma XI

PATENTS (US only)

GL Mosher and DW Miles, Unpublished patent application, filed 2015, Patent Pending

GL Mosher and DW Miles, Unpublished patent application, filed 2015, Patent Pending

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. Publication 2016/0058786, Patent Pending.

JD Pipkin, GL Mosher and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. Publication 2015/0050355, Patent Pending.

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. US Patent 9,125,945 (2015).

GL Mosher, SG Machatha and DJ Cushing, Pharmaceutical Compositions Comprising Prasugrel and Cyclodextrin Derivatives and Methods of Making and Using the Same. Publication 2015/0005341, Patent Pending.

GL Mosher, Stabilized Formulation Containing Iodinated Contrast Agents and Cyclodextrins. Publication 2014/0377185, Patent Pending.

GL Mosher, Stabilized Formulation Containing Iodinated Contrast Agents and Cyclodextrins. Publication 2013/0323181, Patent Pending.

JD Pipkin, RO Zimmerer, DO Thompson and GL Mosher, Inhalant Formulation Containing Sulfoalkyl Ether Cyclodextrin and Corticosteroid. Publication 2013/0303498, Patent Pending.

JD Pipkin, RO Zimmerer, DO Thompson and GL Mosher, Inhalant Formulation Containing Sulfoalkyl Ether Cyclodextrin and Corticosteroid. Publication 2013/0059826, Patent Pending.

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. US Patent 8,853,236 (2014).

GL Mosher, JD Pipkin and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 8,846,901 (2014).

GL Mosher, SG Machatha and DJ Cushing, Pharmaceutical Compositions Comprising Prasugrel and Cyclodextrin Derivatives and Methods of Making and Using the Same. US Patent 8,835,407 (2014).

JD Pipkin, GL Mosher and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 8,829,182 (2014).

JD Pipkin, GL Mosher and DB Hecker, DPI Formulation Containing Sulfoalkyl Ether Cyclodextrin. Publication 2013/0197105, Patent Pending.

GL Mosher, RL Wedel, KT Johnson, SG Machatha, JA Cowee and DJ Cushing, Formulations containing clopidogrel and sulfoalkyl ether cyclodextrin and methods of use. US Patent 8,343,995 (2013).

JD Pipkin, GL Mosher and DB Hecker, DPI Formulation Containing Sulfoalkyl Ether Cyclodextrin. Publication 2012/0164184, Patent Pending.

GL Mosher, SG Machatha and DJ Cushing, Pharmaceutical Compositions Comprising Prasugrel and Cyclodextrin Derivatives and Methods of Making and Using the Same. US Patent 8,236,782 (2012).

JD Pipkin, GL Mosher and DB Hecker, DPI Formulation Containing Sulfoalkyl Ether Cyclodextrin. US Patent 8,114,438 (2012).

GL Mosher, JD Pipkin and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 8,049,003 (2011).

JD Pipkin, GL Mosher and DB Hecker, Sulfoalkyl Ether Cyclodextrin Compositions and Methods of Preparation Thereof. US Patent 7,629,331 (2009).

DO Thompson and GL Mosher, Formulations Containing Propofol and a Sulfoalkyl Ether Cyclodextrin. US Patent 7,034,013 (2006).

GL Mosher, KT Johnson, AA Gayed, and DO Thompson, Formulations Containing Amiodarone and a Sulfoalkyl Ether Cyclodextrin. US Patent 6,869,939 (2005).

VJ Stella, RA Rajewski, MR Venkatramana, JW McGinity, and GL Mosher, Sulfoalkyl Ether

Cyclodextrin Based Controlled Release Solid Pharmaceutical Formulations. US Patent 6,046,177 (2000).

GL Mosher, Absorption Enhancer/Solubilizer Combination for Improved Bioavailability of a Zwitterionic Compound. US Patent 5,525,596 (1996).

GL Mosher and MV Mullen, R-Forms of Cefuroxime Axetil. US Patent 5,063,224 (1991).

PUBLICATIONS

Elizabeth S. Rowe, Vernon D. Rowe, Sangita Biswas, Gerold Mosher, Lovella Insisienmay, Marlies K. Ozias, Michael R. Gralinski, John Hunter, James S Barnett, (2016) Preclinical Studies of Kidney Safe Iodinated Contrast Agent, J. Neuroimaging, May 12, 2016 online.

D Cushing, P Souney, W Cooper, G Mosher, M Adams, S Machatha, B Zhang, and P Kowey, Assessment of the pharmacokinetics and platelet aggregation inhibitory effects of a novel intravenous formulation of clopidogrel in humans, Clin. Exp. Pharm. Physiol., 39: 3-8 (2012).

GL Mosher, VD Antle, and JD Pipkin, Sulfobutylether β -Cyclodextrin, in Handbook of Pharmaceutical Excipients, 7th Edition by Rowe, R.C., Sheskey, P.J. Cook, W.G., and Fenton, M.E., Eds, London:Pharmaceutical Press, 823-826 (2012).

GL Mosher and SG Machatha, Complexation: Cyclodextrins, in Encyclopedia of Pharmaceutical Science and Technology, 4th Edition by Swarbrick, J., New York: Informa Healthcare USA Inc., (2013).

GL Mosher and JD Pipkin, Sulfobutyl Ether β -Cyclodextrin, in Handbook of Pharmaceutical Excipients, 6th Edition by Rowe, R.C., Sheskey, P.J. and Quinn, M.E, Eds, London: Pharmaceutical Press, 714-717 (2009).

GL Mosher and JD Pipkin, Sulfobutyl Ether β -Cyclodextrin, in Handbook of Pharmaceutical Excipients, 5th Edition by Rowe, R.C., Sheskey, P.J. and Owen S.C, Eds, London: Pharmaceutical Press, 754-757 (2006).

G Mosher and DO Thompson, Complexation: Cyclodextrins, in Encyclopedia of Pharmaceutical Technology: Third Edition by Swarbrick, J., New York: Informa Healthcare USA Inc., Volume 2, 671-696 (2006).

GL Mosher and JD Pipkin, Sulfobutyl Ether β -Cyclodextrin, in Pharmaceutical Excipients 2004 by Rowe, R.C., Sheskey, P.J. and Owen S.C, Eds, London: Pharmaceutical Press (2004).

SF Lockwood, S O'Malley and GL Mosher, Improved aqueous solubility of crystalline astaxanthin (3,3'-dihydroxy- β , β -carotene-4,4'-dione) by Captisol[®] (sulfobutyl ether β -cyclodextrin), J. Pharm. Sci., 92(4): 922-926 (2003).

GL Mosher and DO Thompson, Complexation and Cyclodextrins, in Encyclopedia of Pharmaceutical Technology by Swarbrick, J. and Boylan, J.C., New York: Marcel Dekker, Inc., Volume 19, 49-88 (2000).

GL Mosher, The determination of interfacial transfer constants using side-by-side diffusion cells, Pharm. Res., 11(9): 1325-1329 (1994).

GL Mosher, J McBee and DB Shaw, Esterase activity towards the diastereomers of cefuroxime axetil in the rat and dog, Pharm. Res., 19(5): 687-689 (1992).

GL Mosher and J McBee, Photoreactivity of LY277359 maleate, a 5-HT₃ receptor antagonist, in solution, Pharm. Res., 8(10): 1215-1222 (1991).

GL Mosher, H Bundgaard, E Falch, C Larsen, and T Mikkelsen, Ocular bioavailability of pilocarpic acid mono- and diester prodrugs as assessed by miotic activity in the rabbit, Int. J. Pharm., 39: 113-120 (1987).

H Bundgaard, E Falch, C Larsen, GL Mosher and T Mikkelsen, Pilocarpine prodrugs. II. Synthesis, stability, bioconversion, and physicochemical properties of sequentially labile pilocarpic acid diesters, J. Pharm. Sci., 75: 775-783 (1986).

GL Mosher, Theoretical and Experimental Evaluation of Pilocarpine Prodrugs for Ocular Delivery, Dissertation for Doctor of Philosophy, (1986).

GL Mosher, Diethylpropion, a monograph in Chemical Stability of Pharmaceuticals by Connors, Amidon, Kennon and Stella, 2nd Edition, New York: John Wiley and Sons, (1986).

H Bundgaard, E Falch, C Larsen GL Mosher and T Mikkelsen, Pilocarpic acid esters as novel sequentially labile pilocarpine prodrugs for improved ocular delivery, J. Med. Chem., 28: 979-781 (1985).

GL Mosher and TJ Mikkelsen, Permeability of the n-alkyl p-aminobenzoate esters across the isolated corneal membrane of the rabbit, Int. J. Pharm., 2: 239 (1979).

ABSTRACTS/PRESENTATIONS

S Biswas, ES Rowe, G Mosher, MK Ozias, MR Gralinski, and VD Rowe, Veropaque, A Novel Contrast Formulation, Mitigates Contrast Induced Acute Kidney Injury, 24th Annual Transcatheter Cardiovascular Therapeutics Meeting, Miami, FL (Nov 22-26, 2012). Abstract in J Am Coll Cardiol 60(17) Suppl. B :B40 (2012).

JD Pipkin, SG Machatha, GL Mosher, and Q He, Bioequivalence of a Captisol-Enabled[®] fosphenytoin sodium injection formulation to the marketed reference listed product via IV and IM administration in healthy volunteers, 64th Annual Meeting of the American Epilepsy Society, San Antonio, TX (Dec 3-7, 2010).

SG Machatha, C Fulk, GL Mosher and JD Pipkin, The effects of Captisol[®] on the solubilization and stabilization of antiepileptic drugs, 2010 AAPS Annual Meeting and Exposition, New Orleans, LA (Nov 14-18, 2010).

S Biswas, ES Rowe, G Mosher, L Tejada, MK Ozias, and VD Rowe, Nephroprotective effects of substituted cyclodextrins, 15th International Cyclodextrin Symposium, Vienna Austria, (May 9-12, 2010).

SG Machatha, GL Mosher and DJ Cushing, Effects of modified cyclodextrin derivatives on the solubility and stability of prasugrel in aqueous formulations, 2009 AAPS Annual Meeting and Exposition, Los Angeles, CA (Nov 8-12, 2009).

PF Souney, J Cowee, DJ Cushing, G Mosher, and P Holmes, Stability of a cyclodextrin-based IV formulation of amiodarone when diluted with 5 percent dextrose or 0.9 percent sodium chloride injections in both PVC and polyolefin intravenous bags over 7 days, 2009 ASHP Summer Meeting, Rosemont, IL (June 14-17, 2009).

D Cushing, R Lipicky, P Kowey, C Cannon, M Adams, W Cooper and G Mosher, Assessment of the pharmacokinetic and pharmacodynamic effects of intravenous clopidogrel in humans, American College of Cardiology 58th Annual Scientific Session, Orlando, FL (Mar 28-31, 2009).

PF Souney, J Cowee, G Mosher and DJ Cushing, Stability of intravenous amiodarone formulations in glass, polyolefin and polyvinylchloride containers over 72 hours, ASHP Midyear Clinical Meeting, Orlando, FL (Dec 7-11, 2008).

SG Machatha, RL Wedel, KT Johnson and GL Mosher, Effects of modified cyclodextrin derivatives on the solubility and stability of clopidogrel bisulfate in aqueous formulations, 2007 AAPS Annual Meeting and Exposition, San Diego, CA (Nov 10-15, 2007).

PW Holmes, SG Machatha, CF Fulk and GL Mosher, The common ion effect and its impact on the development of a stable Captisol-Enabled[®] fosphenytoin sodium injection formulation, 2007 AAPS

Annual Meeting and Exposition, San Diego, CA (Nov 10-15, 2007).

DJ Cushing, WD Cooper, GL Mosher, MR Gralinski and BW Massey, Pharmacokinetic and pharmacodynamic effects of a novel intravenous formulation of clopidogrel bisulfate, 2007 AAPS Annual Meeting and Exposition, San Diego, CA (Nov 10-15, 2007).

G Mosher, Clinical pharmacokinetics and taste assessment comparison of an aqueous sulfobutylether- β -cyclodextrin based oral formulation of sertraline HCl to Zoloft oral concentrate, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

KT Johnson and G Mosher, Investigation of atypical bi-phasic complexation curves observed when charged cyclodextrins solubilize charged drug compounds, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

R Wedel, A Gayed and GL Mosher, Development of an aqueous-based oral solution formulation of sertraline HCl using sulfobutylether- β -cyclodextrin, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

CF Fulk, A Gayed, B Lund, GL Mosher, DO Thompson and R Wedel, Preserved formulations containing Captisol[®] brand of sulfobutylether- β -cyclodextrin, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

SJ Carter, DA Robaugh, RO Zimmerer, GL Mosher and NJ Cogburn, Overcoming unique challenges in developing a method for the quantitation of sulfobutyl ether β -cyclodextrin in rat and dog plasma by LC/MS, 2004 AAPS Annual Meeting and Exposition, Baltimore, MD (Nov 7-11, 2004).

S Katpally, MK Ghorab, D Thompson, G Mosher, JD Madura and MC Adeyeye, Characterization of bile salt / SBE7- β -cyclodextrin interactions using isothermal titration calorimetry, 2002 AAPS Annual Meeting and Exposition, Montreal Canada (Nov 10-14, 2002).

ML Sirna, CF Fulk, and GL Mosher, Captisol-Enabled[™] Propofol: Formulation approaches to reduce oxidation, 2002 AAPS Annual Meeting and Exposition, Montreal Canada (Nov 10-14, 2002).

A Vargas-Perex, S Katpally, A Jain, G Mosher, D Thompson and MC Adeyeye, Complexation characteristics of sulfobutylether 7- β -cyclodextrin (SBE7-CD) with chenodeoxycholic acid, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

S Katpally, A Vargas-Perez, D Thompson, G Mosher and MC Adeyeye, Complexation characteristics of sulfobutylether- β -cyclodextrin (SBE7-CD) with bile acids, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

KT Johnson and G Mosher, Development and qualification of a fluorescence method for the determination of sulfobutylether-7- β -cyclodextrin delivered in an aerosol inhalation safety study, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

G Mosher, and C Fulk, Co-solvent effects on the rate and extent of solubilization of drugs by Captisol[®] brand of sulfobutyl ether β -cyclodextrin, 2001 AAPS Annual Meeting and Exposition, Denver, CO (Oct 21-25, 2001).

CA Vasquez, NA Neilan and GL Mosher, In vitro evaluation of biocompatibility of a dose formulation, 40th Annual Meeting of the Society of Toxicology, San Francisco, CA, (Mar 25-29, 2001).

C Fulk, SM Ghate, GL Mosher and DO Thompson, Preparation of the ammonium salt of sulfobutyl ether β -cyclodextrin (Captisol[®]) for use in controlled release formulations, 27th International Symposium on Controlled Release of Bioactive Materials, Paris, (July 7-13, 2000).

GL Mosher, Cyclodextrins, they're not just for breakfast any more, Kansas City Discussion Group of Pharmaceutical and Allied Scientists, (Jan 2000).

GL Mosher, S Bradley and E Evans, Continuous IV infusion studies in dogs, Kansas City Discussion Group of Pharmaceutical and Allied Scientists, (1996).

GL Mosher, K Trubitt-Johnson and RC Wood, Absorption enhancer solubilizer combination for improved bioavailability of a zwitterionic compound, 9th Annual AAPS National Meeting, (1994).

SA Sweetana and GL Mosher, Bile salt-insulin interactions. Optical spectroscopy studies. 6th Annual AAPS National Meeting, (1991).

J McBee and GL Mosher, Hydrolysis of four dihydrolysergic acid derivatives using in vitro enzyme systems from the rat and dog, 3rd Annual AAPS National Meeting, (1989).

GL Mosher and T Mikkelsen, An implicit method for modeling the simultaneous transport and metabolism of pilocarpine prodrugs across the excised rabbit cornea, Lilly Modeling Conference, (1987).

GL Mosher, H Bundgaard, E Falch and C Larsen, Effects of drug-protein binding on the precorneal loss of pilocarpine prodrugs, 1st Annual AAPS National Meeting, (1986).

GL Mosher, T Mikkelsen, H Bundgaard, E Falch and C Larsen, Prodrug-to-drug ocular bioconversion of pilocarpic acid diesters, 39th Annual APS Meeting, (1985).

GL Mosher, T Mikkelsen, H Bundgaard, E Falch and C Larsen, Pilocarpine prodrugs. II. Comparative miotic activities of pilocarpic acid esters in the rabbit following topical instillation, 37th Annual APS Meeting, (1984).

H Bundgaard, E Falch, C Larsen, GL Mosher and T Mikkelsen, S Pilocarpine prodrugs. I. Synthesis, physicochemical properties and kinetics of lactonization of pilocarpic acid esters, 37th Annual APS Meeting, (1984).

GL Mosher, Pharmacokinetics - principles and application, Pharmacy Continuing Education Fall Seminar Circuit, University of Kansas, (1984).

GL Mosher, T Mikkelsen and K Himmelstein, Diffusion of a series of homogenous compounds across single and laminated polymeric membranes. 15th Annual Graduate Student Pharmaceutical Research Meeting, (1983).

GL Mosher and T Mikkelsen, Corneal uptake of the n-alkyl p-aminobenzoate homologs, 27th Annual APS National Meeting, (1979)

GL Mosher and T Mikkelsen, Transport across the isolated corneal membrane and physicochemical drug properties, 125th Annual APhA National Meeting, Montreal, Canada (1978).

Attorney Docket No. 43060-707.304
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	MOSHER; Gerold L [Us] et al.	Group Art Unit:	1629
Serial Number:	16/177,159	Examiner:	SPRINGER; Stephanie K.
Filing or 371 (c) Date:	2018-10-31	CONFIRMATION NO:	3572
Title:	ENALAPRIL FORMULATIONS		

FILED ELECTRONICALLY ON: April 19, 2019

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☐ *37 CFR § 1.97 (b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
-- OR --
 - ☐ (3) It is being filed before the mailing of a first Office action on the merits;
-- OR --
 - ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☒ *37 CFR § 1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in § 1.97 (e) provided concurrently herewith;
-- OR --
 - ☒ a fee of \$240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR § 1.97 (d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
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- D. ☐ *37 CFR § 1.97 (e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
-- AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
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- H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$240.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.43060-707.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: April 19, 2019

By: /Clark Lin/

Clark Y. Lin, Ph.D., Esq.
Registration No. 67,024

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 02-1971

Attorney Docket No. 43060-707.304
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: MOSHER; Gerold L [Us] et al. Serial Number: 16/177,159 Filing or 371 (c) Date: 2018-10-31 Title: ENALAPRIL FORMULATIONS	Group Art Unit: 1629 Examiner: SPRINGER; Stephanie K. CONFIRMATION NO: 3572
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FILED ELECTRONICALLY ON: April 19, 2019

Commissioner for Patents
P.O. Box 1450
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INFORMATION DISCLOSURE STATEMENT
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- ☐ a statement as specified in § 1.97 (e) provided concurrently herewith;
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 - ☒ a fee of \$240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR § 1.97 (d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
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Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: April 19, 2019

By: /Clark Lin/

Clark Y. Lin, Ph.D., Esq.
Registration No. 67,024

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 02-1971

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	10/31/2018	Gerold L. Mosher	43060-707.304	3572
<div> <div>21971759006/24/2019</div> <div>WILSON, SONSINI, GOODRICH & ROSATI</div> <div>650 PAGE MILL ROAD</div> <div>PALO ALTO, CA 94304-1050</div> </div>			<div>EXAMINER</div> <div>SPRINGER, STEPHANIE K</div>	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			06/24/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary**Application No.**

16/177,159

Applicant(s)

Mosher et al.

Examiner

STEPHANIE K SPRINGER

Art Unit

1629

AIA (FITF) Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 1 March 2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a) ☒ This action is **FINAL**.

2b) ☐ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-11,13-26 and 28-30 is/are pending in the application.

5a) Of the above claim(s) ____ is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1-11,13-26 and 28-30 is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date ____.

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: ____.

Paper No(s)/Mail Date 14 pgs, 4/19/19.

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DETAILED ACTION

Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

This application is a continuation of application 16/003,994, now US Patent 10,154,987, filed on June 8, 2018, which is a continuation of application 15/802,341, now US Patent 10,039,745, filed on November 2, 2017, which is a continuation of application 15/613,622, now US Patent 9,808,442, filed on June 5, 2017, which is a continuation of application 15/081,603, now US Patent 9,669,008, filed on March 25, 2016 and claims priority to US provisional application 62/310,198, filed on March 18, 2016.

This application was granted Track One status on December 14, 2018.

Applicant's amendments filed March 1, 2019 amending claims 1, 14, 17, and 18, and canceling claims 12 and 27 are acknowledged.

Applicant's arguments, filed March 1, 2019, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn.

Claims 1-11, 13-26, and 28-30 are pending and are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on April 19, 2019 has been considered by the examiner. The submission is in compliance with the provisions of 37 CFR §§ 1.97 and 1.98. Enclosed with this Office Action is a return-copy of the Forms PTO-1449 with the examiner's initials and signature indicating those references that have been considered.

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Response to Arguments

Declaration under 37 CFR 1.132

The Declaration under 35 CFR 1.132 submitted on March 1, 2019 has been considered by the Examiner. The declaration under 37 CFR 1.132 is insufficient to overcome the rejections of claims 1-11, 13-26, and 28-30, as it fails to provide data corroborating the Applicant's allegations that the claimed compositions provide unexpected results over the compositions disclosed in the prior art.

The Declaration, dated February 2, 2017, is directed towards application 15/081,603, now US Patent 9,669,008. The Declaration alleges that the enalapril oral liquid formulations of '603 "provides several advantages", particularly improved ease of administration; patient compliance; and accuracy of dosing. The Declaration contends that the enalapril oral liquid formulations "of the present claims", that is, the claims of '603, are stable at 5 ± 3 °C for 12 months or longer with minimal degradation.

The Declaration presents exemplary formulations E7 and E8:

Composition of Enalapril Maleate Formulations		
Component	E7	E8
Enalapril maleate	1.00	1.00
Citric acid anhydrous	1.80	1.82
Sodium citrate anhydrous	0.16	0.15
Sodium benzoate	1.00	1.00
Sucralose	0.70	0.70
Mixed berry flavor	0.50	0.50
Water	qs	qs
pH (measured)	3.3	3.3
qs = sufficient quantity		

It appears that these refer to percentages of the total composition. Thus, formulations E7 and E8 are directed to aqueous compositions comprising

- a) enalapril maleate in an amount of 1.00%;
- b) citric acid and sodium citrate in a total amount of 1.96% or 1.97%;

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- c) sodium benzoate in an amount of 1.00%;
- d) sucralose in an amount of 0.70%;
- e) flavoring in an amount of 0.50%.

The Applicant's attention is directed towards MPEP § 716.02, Allegations of Unexpected Results: "Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected."

In order to demonstrate unexpected results, a comparison between the claimed invention and the closest prior art must be evaluated. By way of comparative examples, the Applicant offers compositions representing Nahata, prepared using a) water, b), either citrate buffer at a pH of 5.0, or c) a 1:1 mixture of Ora-Plus and Ora-Sweet (Tables A and B, Figures 1 and 2).

While Applicant has provided evidence demonstrating the unexpected stability of formulations E7 and E8 as compared to the compositions of Nahata, the formulations E7 and E8 are essentially identical, and limited to a single embodiment of the claimed invention. The Examiner notes that the instantly claimed invention is drawn to aqueous compositions comprising

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising citric acid and sodium citrate, in any amount and in any ratio; and

(iii) one of over twenty recited preservatives, in any amount.

The inventive compositions of E7 and E8 are limited to compositions comprising a single, specific amount of enalapril; a single, specific amount and ratio of citric acid and sodium citrate; and a single, specific preservative (sodium benzoate) in a specific amount.

Thus, Applicant has failed to provide data supporting the breadth of the claims. MPEP § 716.02(d) addresses the subject of unexpected results commensurate in scope with the claimed invention: "Whether the unexpected results are the result of unexpectedly improved results or a

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property not taught by the prior art, the “objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.” In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. See *In re Peterson*, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir.1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims.). However, the subject matter circumscribed by the instant claims extends well beyond the metes and bounds of these discrete embodiments potentially demonstrated to exert unexpected results over the prior art compositions, as the Applicant has proffered a single aqueous composition comprising a) enalapril maleate in an amount of 1.00%; b) citric acid and sodium citrate in a total amount of 1.96% or 1.97%; and c) sodium benzoate in an amount of 1.00%. As the instant claims are drawn to compositions comprising (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer comprising citric acid and sodium citrate, in any amount and in any ratio; and (iii) one of over twenty recited preservatives, in any amount, the claims are not commensurate in scope with the disclosed embodiments. Applicant has failed to address why the data from the exemplified combinations are indicative of unexpected results over the entire scope of subject matter instantly claimed.

New Grounds of Rejection

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of

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the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), first paragraph:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13-26, and 28-30 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is distinct from the enablement requirement; this was first pointed out by the court in *In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967), and clarified in *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). The issue of whether the claimed subject matter is adequately supported/described by the specification, is a question of fact. *Id.* at 1563, 19 USPQ2d at 1116.

When considering whether the claimed subject matter complies with the written description requirement, Applicants' disclosure should be read in light of the knowledge possessed by those skilled in the art. See *In re Lange*, 644 F.2d 856, 863, 209 USPQ 288, 294. See also, *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

Applicants enjoy the presumption that their patent application is valid and all statements contained therein are accurate; it is the PTO's burden to demonstrate why any of Applicants' claims should be rejected or why any of Applicant's statements should be doubted. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370. If successful in presenting such evidence

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and argument, the burden then shifts to the Applicant to provide evidence that would convince one to the contrary.

The instantly claimed invention is generally drawn to compositions comprising:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising citric acid and sodium citrate;

(iii) a preservative selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and

(iv) water.

The Examiner notes that while the claims limit the amount of enalapril, the buffer and the preservative are present in the formulations in any amount.

The claimed invention allegedly provides for formulations which are stable at about 5 ± 3 °C for at least 12 months, having about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period, as recited in independent claims 1, 17, and 18. Allegedly, the recited properties of stability are the result of the instantly claimed combinations of active agent, buffer, preservative, and water.

Turning to the specification, the specification discloses certain working embodiments representing the claimed formulations.

Table A-1 (page 36) is directed towards liquid formulations comprising

(i) 1.0 mg/ml enalapril maleate;

(ii) a buffer comprising 5-12 mM of a mixture of citric acid and sodium citrate;

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(iii) 1 mg/mL sodium benzoate; 1 mg/mL sodium benzoate and 1.75 mg/mL methylparaben sodium; or 0.335 mg/mL methylparaben sodium, 0.095 mg/mL propylparaben sodium, and 1 mg/mL potassium sorbate; and

(iv) water.

Table B-1 (pages 37-38) is directed towards liquid formulations comprising

(i) 1.0 mg/ml enalapril maleate;

(ii) a buffer comprising 1-4 mg/mL sodium citrate;

(iii) 1 mg/mL sodium benzoate; and

(iv) water.

The formulations of Tables A-1 and B-1 are evaluated after heating at 60 °C. There is no disclosure directed towards the formulations of Table A-1 at the recited storage conditions of 5 ± 3 °C for at least 12 months. Accordingly, the formulations of Tables A-1 and B-1 are not relevant to the instantly claimed invention.

Table C-1 (page 39) is directed towards formulations formed by dissolving a powder formulation of enalapril in water; the resulting liquid formulations comprise

(i) 1.0 mg/ml enalapril maleate;

(ii) a buffer comprising 4 to 4.4 mg/mL sodium citrate;

(iii) 0.34 mg/mL sodium methylparaben, 0.09 mg/mL sodium propylparaben, and 1.0 mg/mL potassium sorbate; 1.0 mg/mL sodium methylparaben, 1.0 mg/mL sodium propylparaben, and 1.0 mg/mL sodium benzoate; or 1.0 mg/mL sodium methylparaben and 1.0 mg/mL sodium benzoate; and

(iv) water.

The formulations of Table C-1 are evaluated under storage conditions of 5 ± 3 °C for up to 8 weeks. However, the instantly claimed invention requires stability for up to 12 months, and thus, Table C-1 does not appear relevant to the claimed invention.

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Table D-1 (page 41) is also directed towards formulations formed by dissolving a powder formulation of enalapril in water; the resulting liquid formulations comprise

- (i) 1.0 mg/ml enalapril maleate;
- (ii) a buffer comprising 4 to 4.28 mg/mL sodium citrate;
- (iii) 1.0 mg/mL sodium benzoate; and
- (iv) water.

The formulations of Table D-1 are evaluated under storage conditions of 5 ± 3 °C for up to 26 weeks. Again, the instantly claimed invention requires stability for up to 12 months, and thus, Table D-1 does not appear relevant to the claimed invention.

Table E-1 (page 43) is directed towards liquid formulations comprising

- (i) 1.0 mg/ml enalapril maleate;
- (ii) a buffer comprising 1 to 4 mg/mL of a mixture of citric acid and sodium citrate;
- (iii) 1 mg/mL sodium benzoate; and
- (iv) water.

The formulations of Table D-1 are evaluated under storage conditions of 5 ± 3 °C for up to 62 weeks.

Table G-1 (page 45) is directed towards liquid formulations comprising

- (i) 1.0 mg/ml enalapril maleate;
- (ii) a buffer comprising 1.8 to 1.96 mg/mL of a mixture of citric acid and sodium citrate;
- (iii) 0.40 to 1 mg/mL sodium benzoate; and
- (iv) water.

There is no disclosure regarding evaluation of storage conditions of the formulations of G-1, and thus, Table G-1 is not pertinent to the claimed invention.

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Thus, the specification disclosed formulations of Table D-1 and evidence demonstrating that the formulations of Table D-1 provide the recited properties of at about 5 ± 3 °C for at least 12 months, having about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period. The Declaration filed March 1, 2019 also provides working embodiments of the claimed invention. The Declaration dated February 2, 2017, is directed towards application 15/081,603, now US Patent 9,669,008. The Declaration provides embodiments of a single aqueous composition comprising a) enalapril maleate in an amount of 1.00%; b) citric acid and sodium citrate in a total amount of 1.96% or 1.97%; and c) sodium benzoate in an amount of 1.00%. The comparative formulations of Nahata are evaluated under storage conditions of 5 ± 3 °C for up to 91 days. The inventive formulation of E8 is only evaluated up to 42 days; the inventive formulation of E7 is evaluated up to 581 days (Table A, page 5).

Accordingly, the specification and declaration provide working embodiments of liquid aqueous compositions comprising

(i) 1.0 mg/mL enalapril maleate; (ii) a buffer comprising 1 to 4 mg/mL of a mixture of citric acid and sodium citrate; and (iii) 1 mg/mL sodium benzoate;

(i) 1.0 mg/mL enalapril maleate; b) a buffer comprising 1.96-1.97 mg/mL of a mixture of citric acid and sodium citrate; and (iii) 1 mg/mL sodium benzoate.

The Examiner again notes that when considering whether the claimed subject matter complies with the written description requirement, Applicants' disclosure should be read in light of the knowledge possessed by those skilled in the art. See *In re Lange*, 644 F.2d 856, 863, 209 USPQ 288, 294. See also, *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

The state of the art at the time of the invention suggests that while liquid formulations of enalapril were well known at the time of the invention, the long term storage stability of said

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formulations was not disclosed. Nahata et al., "Stability of enalapril maleate in three extemporaneously prepared oral liquids", *Am. J. Health-Syst. Pharm.*, 1998, vol. 55, pages 1155-1157 (cited in PTO-892 dated January 25, 2019) is the closest prior art.

Nahata teaches formulations comprising

- (i) 1 mg/ml enalapril;
- (ii) a buffer comprising citric acid and sodium citrate;
- (iii) a preservative, such as citric acid, sodium chloride, and
- (iv) water.

Nahata also teaches an aqueous solution comprising 1 mg/ml enalapril in a mixture of Ora-Sweet and Ora-Plus (page 1156, column 1, paragraph 2). Ora-Sweet and Ora-Plus are commercially available from Paddock Laboratories (page 1157, footnotes d and e). Ora-Sweet is an aqueous solution comprising sucrose, glycerin, sorbitol, flavoring, citric acid, sodium phosphate, methylparaben, and potassium sorbate; Ora-Plus is an aqueous solution comprising microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, flavoring, citric acid, sodium phosphate, simethicone, methylparaben, and potassium sorbate; both Ora-Sweet and Ora-Plus have a pH of 4.2. Thus, the formulation taught by Nahata comprising 1 mg/ml enalapril in a mixture of Ora-Sweet and Ora-Plus comprises

- (i) 1 mg/ml enalapril;
- (ii) citric acid;
- (iii) a preservative, such as citric acid, methylparaben, potassium sorbate; and
- (iv) water.

The formulations comprising Ora-Sweet and Ora-Plus also comprise sweeteners and flavoring agents, while not containing mannitol or silicon dioxide.

Although Nahata does not explicitly teach that the formulation is stable at about 5 ± 3 °C for at least 12 months, or that the formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given

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storage period, the formulations taught by Nahata generally meet the requirements of the instantly claimed invention. However, the Declaration and remarks filed March 1, 2019, contend that the instantly claimed formulations provide unexpected stability over the prior art formulations.

Regarding the requirement for adequate written description, Applicant's attention is directed to MPEP § 2163. In particular, *Regents' of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106. Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

The specification and declaration provide working embodiments representing the instantly claimed invention in the form of liquid aqueous compositions comprising

(i) 1.0 mg/mL enalapril maleate; (ii) a buffer comprising 1 to 4 mg/mL of a mixture of citric acid and sodium citrate; and (iii) 1 mg/mL sodium benzoate;

(i) 1.0 mg/mL enalapril maleate; b) a buffer comprising 1.96-1.97 mg/mL of a mixture of citric acid and sodium citrate; and (iii) 1 mg/mL sodium benzoate.

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While such disclosure has been acknowledged, it is noted that the claimed subject matter extends far beyond these select embodiments potentially demonstrated to have unexpected long-term stability as compared to the formulations of Nahata. The instant claims are drawn to compositions comprising (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer comprising citric acid and sodium citrate, in any amount and in any ratio; and (iii) one of over twenty recited preservatives, in any amount. However, Applicant has failed to provide a limiting definition via the disclosure of relevant structural characteristics or physical properties that would provide adequate written description of the genus of formulations capable of achieving the required long-term stability to demonstrate that Applicant was actually in possession of the breadth of the claimed invention at the time of the invention.

MPEP § 2163 recites, "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus." The Applicant's attention is directed to *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Although the Applicants have disclosed a select number of embodiments of the claimed invention, there is no disclosure, either explicitly or with sound basis to support the breadth of the claimed invention, particularly the allegedly unexpected long-term stability that Applicant contends is the inventive concept of the claimed formulations. Although one would generally recognize that a preservative could be substituted for another preservative, Applicant has failed to provide a limiting definition via the disclosure of relevant physical properties as being responsible for the function of the formulation that would provide adequate written description of the genus of formulations which would be stable at about 5 ± 3 °C for at least 12 months, having

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about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period. Thus, Applicants have not adequately described the invention for the breadth that is claimed. It thus appears that Applicants were not in possession of the claimed invention at the time the application was filed, the boundaries of the genus have not been adequately set forth, and the limited number of exemplified compositions would not support the breadth of the claimed genus.

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Maintained Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the

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scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,669,008, herein referred to as '008. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-20 of '008 are generally drawn towards stable oral liquid formulations comprising enalapril, a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Claim 18 is drawn to a particular species of composition, namely, a stable oral liquid formulation, consisting essentially of: (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml sodium benzoate; (v) a flavoring agent; (vi) water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-20 of '008 are drawn to a species of the instantly claimed formulation. The ordinarily skilled

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artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-20 of '008.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '008.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 9,808,442, herein referred to as '442. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-30 of '442 are generally drawn towards methods of treating hypertension, heart failure, and left ventricular dysfunction in a subject, comprising administering a stable oral liquid formulation comprising enalapril; a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-30 of '442 are drawn to methods of use of a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-30 of '442.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '442.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 10,039,745, herein referred to as '745. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-20 of '745 are generally drawn towards stable oral liquid formulations comprising enalapril, a buffer comprising citric acid and sodium citrate dehydrate; a preservative

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that is sodium benzoate; and water; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-20 of '745 are generally drawn towards a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-20 of '745.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '745.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 10,154,987, herein referred to as '987. Although the claims at issue are not identical, they are not patentably distinct from each other.

Claims 1-30 of '987 are generally drawn towards methods of treating hypertension, heart failure, and left ventricular dysfunction in a subject, comprising administering a stable oral liquid formulation comprising enalapril; a buffer comprising citric acid and sodium citrate dehydrate; a preservative that is sodium benzoate; and water; wherein the pH of the formulation is less than about 3.5; wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. Thus, claims 1-30 of '987 are drawn to a method of using a species of the instantly claimed formulation. The ordinarily skilled artisan would find it *prima facie* obvious to arrive at the instantly claimed invention in view of the methods of use described in claims 1-30 of '987.

Accordingly, the instantly claimed invention is an obvious variant of the invention claimed in '987.

Response to Arguments

Applicant has stated that Applicant has submitted terminal disclaimers with respect to US Patent Nos. 9,669,008; 9,808,442; 10,039,745; and 10,154,987. However, a terminal disclaimer has not been filed. Further, the Applicant failed to provide remarks directed at the propriety of the

Application/Control Number: 16/177,159
Art Unit: 1629

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double patenting rejection itself. In view of this, and the fact that no patentable subject matter has yet been identified, the obviousness double patenting rejections are hereby **maintained**.

Conclusion

No claims are allowed in this application.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Springer whose telephone number is 571-270-7380. The examiner can normally be reached on Monday through Thursday from 8 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren, can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-270-8380.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Page 19

/Stephanie Springer/
Examiner, Art Unit 1629

/JEFFREY S LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

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10154987

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

☐ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

☐ Small Entity

☐ Micro Entity

☒ Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

☒ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 67024

☐ A sole inventor

☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

☐ A joint inventor; all of whom are signing this request

Signature	/Clark Lin/
Name	Clark Y. Lin

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Doc Code: DISQ.E.FILE

Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16177159

Filing Date: 31-Oct-2018

Applicant/Patent under Reexamination: Mosher

Electronic Terminal Disclaimer filed on August 1, 2019

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Doc Code: A.NE.AFCP

Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0		
Practitioner Docket No.: 43060-707.304	Application No.: 16/177,159	Filing Date: October 31, 2018
First Named Inventor: Gerold L. MOSHER	Title: ENALAPRIL FORMULATIONS	
<p>APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.</p> <ol style="list-style-type: none"> 1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (e.g., a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c). 2. The above-identified application contains an outstanding final rejection. 3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect. 4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection. 5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response. 6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web). 7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, e.g., extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.] 8. By filing this certification and request, applicant acknowledges the following: <ul style="list-style-type: none"> • Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0. • The examiner will verify that the AFCP 2.0 submission is compliant, i.e., that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions: <ul style="list-style-type: none"> ○ The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, e.g., by mailing an advisory action. ○ If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview. <ul style="list-style-type: none"> ▪ The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate. ▪ If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116. 		
Signature /Clark Lin/	Date August 1, 2019	
Name (Print/Typed) Clark Y. Lin	Practitioner Registration No. 67,024	
<p>Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.</p>		
<input checked="" type="checkbox"/> * Total of <u>1</u> forms are submitted.		

SLVGT-EPA_0106720

Electronically Filed: August 1, 2019

Attorney Docket No.: 43060-707.304

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 3572
Serial No.: 16/177,159	Examiner: SPRINGER, Stephanie K.
Filed: October 31, 2018	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<hr/> <p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on August 1, 2019, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u> /Rose Andico/ </u> Rose Andico</p>

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Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

RESPONSE TO FINAL OFFICE ACTION WITH REQUEST FOR CONSIDERATION
UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM

Dear Commissioner:

This paper is a response to the Final Office Action mailed on June 24, 2019. The Commissioner is hereby authorized to charge any fees associated with the filing of this response to Deposit Account No. 23-2415, referencing Docket No. 43060-707.304.

Prior to reconsidering this application on the merits, please amend the application as follows:

Amendments to the Claims begin on page **2**.

Remarks begin on page **6**.

The **Conclusion** is on page **8**.

Amendments to the Claims

This listing of claims will replace all prior versions, amendments and listings of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicant reserves the right to pursue the subject matter of the withdrawn claims in this or any other appropriate patent application.

Listing of the Claims:

1. (Currently Amended) A stable oral liquid formulation, comprising:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate;

(iii) about 1 mg/ml[[a]] preservative, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

2. (Previously Presented) The stable oral liquid formulation of claim 1 further comprising a sweetener.

3. (Previously Presented) The stable oral liquid formulation of claim 2, wherein the sweetener is sucralose.

4. (Previously Presented) The stable oral liquid formulation of claim 1 further comprising a flavoring agent.

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5. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
6. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
7. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the buffer comprises about 0.8 to about 3.5 mg/ml citric acid.
8. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the buffer comprises about 0.1 to about 0.8 mg/ml sodium citrate.
9. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is less than about 3.5.
10. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.
11. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is about 3.3.
12. (Canceled)
13. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the preservative is sodium benzoate.
14. (Canceled)
15. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 18 months.
16. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 24 months.
17. (Currently Amended) A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate;

(iii) about 1 mg/ml[[a]] preservative, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

18. (Currently Amended) A stable oral liquid formulation, comprising:

(i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate;

(iii) about ~~19.3% to about 30%~~ 1% (w/w of solids) of a preservative, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

19. (Previously Presented) The stable oral liquid formulation of claim 18 further comprising a sweetener.

20. (Previously Presented) The stable oral liquid formulation of claim 19, wherein the sweetener is sucralose.

U.S. Patent Application No. 16/177,159

Attorney Docket No.: 43060-707.304

Response to the Final Office Action dated June 24, 2019

21. (Previously Presented) The stable oral liquid formulation of claim 18 further comprising a flavoring agent.
22. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the formulation does not contain mannitol.
23. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the formulation does not contain silicon dioxide.
24. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the pH of the stable oral liquid formulation is less than about 3.5.
25. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.
26. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the pH of the stable oral liquid formulation is about 3.3.
27. (Canceled)
28. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the preservative is sodium benzoate.
29. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 18 months.
30. (Previously Presented) The stable oral liquid formulation of claim 18, wherein the formulation is stable at about $5 \pm 3^{\circ}$ C for at least 24 months.

Electronically Filed: August 1, 2019

Attorney Docket No.: 43060-707.304

REMARKS

Claims 1-11, 13, 15-26, and 28-30 are pending in this application. By way of this response, claims 1, 17, and 18 have been amended, and claim 14 has been canceled. No new matter is presented by way of the amendments.

Withdrawal of any subject matter herein does not constitute an admission that the subject matter is unpatentable for any reason and Applicant reserves the right to file claims directed to withdrawn subject matter in this or a related application.

Rejection Under 35 U.S.C. §112(a)

Claims 1-11, 13, 15-26, and 28-30 are rejected under 35 U.S.C. § 112(a) as failing to comply with the written description requirement. Specifically, the Office noted that “while the claims limit the amount of enalapril, the buffer and the preservative are present in the formulations in any amount.”

Without acquiescing to the Office’s rejection but solely in an effort to expedite prosecution, claims 1 and 17 have been amended to recite “(ii) a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate; (iii) about 1 mg/ml preservative, wherein the preservative is....” Claim 18 has been amended similarly in a % w/w format.

Accordingly, Applicant respectfully requests the rejections be withdrawn.

Double Patenting Objection

Claims 1-11, 13, 15-26, and 28-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,669,008, claims 1-30 of U.S. Patent No. 9,808,442, claims 1-20 of U.S. Patent No. 10,039,745, and claims 1-30 of U.S. Patent No. 10,154,987.

Without acquiescing in this ground of rejection and solely in an effort to expedite prosecution, Applicant hereby submits Terminal Disclaimers with respect to U.S. Patent No. 9,669,008, U.S. Patent No. 9,808,442, U.S. Patent No. 10,039,745, and U.S. Patent No. 10,154,987, as well as U.S. Appl. Ser. No. 16/242,898.

The Terminal Disclaimers obviate the present rejections. Accordingly, Applicant respectfully requests that the rejections be withdrawn.

U.S. Patent Application No. 16/177,159

Attorney Docket No.: 43060-707.304

Response to the Final Office Action dated June 24, 2019

In view of the remarks and amendments submitted herein, Applicant believes that the Application is in condition for allowance and such action is earnestly solicited.

* * *

U.S. Patent Application No. 16/177,159

Attorney Docket No.: 43060-707.304

Response to the Final Office Action dated June 24, 2019

CONCLUSION

Applicant submits that this response fully addresses the Office Action mailed on June 24, 2019. Applicant believes that for the reasons set forth herein the pending claims are in condition for allowance and early and favorable consideration is respectfully requested.

Should the Examiner have any questions or concerns, the Examiner is encouraged to contact the undersigned attorney at (617) 598-7823.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: August 1, 2019

By: /Clark Lin/
Clark Y. Lin, Ph.D., Esq.
Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2306
Customer No. 021971

Attorney Docket No. 43060-707.304
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	MOSHER; Gerold L. et al.	Group Art Unit:	1629
Serial Number:	16/177,159	Examiner:	SPRINGER, Stephanie K.
Filing or 371 (c) Date:	2018-10-31	CONFIRMATION NO:	3572
Title:	ENALAPRIL FORMULATIONS		

FILED ELECTRONICALLY ON: August 23, 2019

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☐ *37 CFR § 1.97 (b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
- OR --
- ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
- OR --
- ☐ (3) It is being filed before the mailing of a first Office action on the merits;
- OR --
- ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☒ *37 CFR § 1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☒ a statement as specified in § 1.97 (e) provided concurrently herewith;
- OR --
- ☐ a fee of \$240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR § 1.97 (d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
- AND --
- ii. a fee of \$240.00 as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☒ *37 CFR § 1.97 (e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
- AND/OR --
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
- AND/OR --
- ☒ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☐ *Statement Under 37 C.F.R. §1.704(d)*. Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☒ *37 CFR §1.98 (a) (2)*. The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☐ *37 CFR §1.98(a)(3)*. The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
- OR --
- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☐ *37 CFR §1.98(d)*. Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$0.00 and/or charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.43060-707.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: September 3, 2019

By: /Clark Lin/

Clark Y. Lin, Ph.D., Esq.
Registration No. 67,024

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971



UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	10/31/2018	Gerold L. Mosher	43060-707.304	3572
21971 7590 09/16/2019 WILSON, SONSINI, GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 94304-1050			EXAMINER SPRINGER, STEPHANIE K	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			09/16/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Advisory Action Before the Filing of an Appeal Brief	Application No. 16/177,159	Applicant(s) Mosher et al.	
	Examiner STEPHANIE K SPRINGER	Art Unit 1629	AIA (FITF) Status Yes

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 August 2019 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:

a) ☐ The period for reply expires ____ months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires ____ months from the mailing date of the prior Advisory Action or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANTS FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because

a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);

b) ☒ They raise the issue of new matter (see NOTE below);

c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet (See 37CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicants reply has overcome the following rejection(s): _____

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☒ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____

9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.

13. ☐ Note the attached Information *Disclosure Statement(s)*. (PTO/SB/08) Paper No(s). _____

14. ☒ Other: See attached PTO-2323.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: 1-11, 13-26 and 28-30.

Claim(s) withdrawn from consideration: _____

/JEFFREY S LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629	
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Continuation of 3. NOTE: The proposed amendments filed 1 August 2019 under AFCP are not entered as they present new issues that require further consideration and/or search, as the amendment proposes introducing further limitations not previously presented for examination. If the proposed amendments were entered, the Examiner would be required to reevaluate the claims for patentability, including a new search to determine whether the newly added limitations are a novel, unobvious limitation. In particular, the recited range of a buffer comprising "about 1-4 mg/ml of a mixture" of citric acid and sodium citrate and "about 1 mg/ml preservative" introduces new limitations which were not recited in the previous claims.

Further, the new limitations raise the issue of new matter, as the newly added limitations are not properly supported in the specification as filed. There is no disclosure of a range of about 1-4 mg/ml of a buffer, let alone the claimed 1-4 mg/ml mixture of citric acid and sodium citrate. Regarding the preservative, while there is support for about 1 mg/ml of a preservative that is either sodium benzoate or a paraben, there is insufficient support for the use of 1 mg/ml of all of the recited preservatives. Because the amendment raises new issues that require further consideration and/or search, they are not deemed to place the application in better form for appeal because they do not materially reduce or simplify the issues for appeal.

Applicant is reminded that when an amendment is filed, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment. In the reply filed 1 August 2019 under AFCP, Applicant merely asserts "no new matter is presented by way of the amendments".

Pursuant with the guidelines of the AFCP 2.0 program, the Examiner has determined that further search and/or consideration would be required if the proposed amendments were entered and that such search and/or consideration cannot be completed by the Examiner in the time allotted under the AFCP 2.0 program.

Continuation of REQUEST FOR RECONSIDERATION/OTHER 12. The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Applicant's request for reconsideration of the present application with regard to the rejections of record in light of the remarks presented in the after final remarks submitted on 1 August 2019 have been made. Applicant's remarks directed towards the obviation of the rejections of record are not found persuasive, because they are predicated, at least in part, on the entry of the proposed amendments. In particular, a new search and examination is required, as the limitations regarding the concentration range of the preservative and the buffer was not previously presented for examination.

Additionally, as noted supra, the proposed amendments appear to introduce new matter, as there is no disclosure in the specification regarding the recited range of "about 1-4 mg/ml mixture of a mixture of citric acid and sodium citrate" or "about 1 mg/ml preservative", unless the preservative is limited to sodium benzoate or a paraben.

As the amendments are not entered, the rejections are maintained for the reasons set forth at pages 3-14 of the Office Action dated June 24, 2019. As noted therein, the disclosed embodiments do not provide adequate evidence of possession of the instantly claimed invention, as the disclosed embodiments are directed towards specific combinations of formulations comprising enalapril maleate, citric acid, sodium citrate, sodium benzoate, and water in specific amounts. The Examiner notes that the Declaration is directed towards application 15/081,603, now US Patent 9,669,008. The example disclosed therein is insufficient to address the breadth of the instant claims.

Accordingly, the 112, 1st paragraph rejection due to a lack of adequate written description for the claimed product is maintained.

<i>Examiner-Initiated Interview Summary</i>	Application No. 16/177,159	Applicant(s) Mosher et al.	
	Examiner STEPHANIE K SPRINGER	Art Unit 1629	AIA (FITF) Status Yes

All participants (applicant, applicant's representative, PTO personnel):

(1) STEPHANIE K. SPRINGER. (3) ____.

(2) Clark Lin. (4) ____.

Date of Interview: 22 August 2019.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: ____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☐ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: ____.

Identification of prior art discussed: ____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Pursuant to the guidelines of AFCP, the Examiner informed Applicant's representative that the amendments would not be entered, and an Advisory Action would be issued..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JEFFREY S LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629	
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AFCP 2.0 Decision

Application No.

16/177,159

Applicant(s)

Mosher et al.

Examiner

STEPHANIE K SPRINGER

Art Unit

1629

AIA (FITF) Status

Yes

This is in response to the After Final Consideration Pilot request filed 01 August 2019.

1. **Improper Request** – The AFCP 2.0 request is improper for the following reason(s) and the after final amendment submitted with the request will be treated under pre-pilot procedure.

- ☐ An AFCP 2.0 request form PTO/SB/434 (or equivalent document) was not submitted.
- ☐ A non-broadening amendment to at least one independent claim was not submitted.
- ☐ The request is not the first proper AFCP 2.0 request submitted in response to the most recent final rejection.
- ☐ Other: _____

2. **Proper Request**

- A. After final amendment submitted with the request will not be treated under AFCP 2.0.

The after final amendment cannot be reviewed and a search conducted within the guidelines of the pilot program.

- ☐ The after final amendment will be treated under pre-pilot procedure.

- B. Updated search and/or completed additional consideration.

The examiner performed an updated search and/or completed additional consideration of the after final amendment within the time authorized for the pilot program. The result(s) of the updated search and/or completed additional consideration are:

- ☐ 1. All of the rejections in the most recent final Office action are overcome and a Notice of Allowance is issued herewith.
- ☒ 2. The after final amendment would not overcome all of the rejections in the most recent final Office action. See attached interview summary for further details.
- ☒ 3. The after final amendment was reviewed, and it raises a new issue(s). See attached interview summary for further details.
- ☐ 4. The after final amendment raises new issues, but would overcome all of the rejections in the most recent final Office action. A decision on determining allowability could not be made within the guidelines of the pilot. See attached interview summary for further details, including any newly discovered prior art.
- ☐ 5. Other: _____

Examiner Note: Please attach an interview summary when necessary as described above.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL (Submitted Only via EFS-Web)							
Application Number	16/177,159	Filing Date	2018-10-31	Docket Number (if applicable)	43060-707.304	Art Unit	1629
First Named Inventor	Gerold L. Mosher, et. al.			Examiner Name	Springer, Stephanie K.		
This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application. Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV							
SUBMISSION REQUIRED UNDER 37 CFR 1.114							
Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).							
<input type="checkbox"/> Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked. <div style="margin-left: 40px;"> <input type="checkbox"/> Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____ <input type="checkbox"/> Other _____ </div>							
<input checked="" type="checkbox"/> Enclosed <div style="margin-left: 40px;"> <input checked="" type="checkbox"/> Amendment/Reply <input type="checkbox"/> Information Disclosure Statement (IDS) <input type="checkbox"/> Affidavit(s)/ Declaration(s) <input type="checkbox"/> Other _____ </div>							
MISCELLANEOUS							
<input type="checkbox"/> Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)							
<input type="checkbox"/> Other _____							
FEES							
<input checked="" type="checkbox"/> The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed. The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No <u>232415</u>							
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED							
<div style="border: 2px solid black; padding: 5px;"> <input checked="" type="checkbox"/> Patent Practitioner Signature <input type="checkbox"/> Applicant Signature </div>							

Signature of Registered U.S. Patent Practitioner			
Signature	Clark Lin/	Date (YYYY-MM-DD)	2019-10-24
Name	Clark Y. Lin	Registration Number	67024

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronically Filed: October 24, 2019

Attorney Docket No.: 43060-707.304

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 3572
Serial No.: 16/177,159	Examiner: SPRINGER, Stephanie K.
Filed: October 31, 2018	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<hr/> <p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on October 24, 2019, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u> /Paula Derby/ </u> Paula Derby</p>

Mail Stop AF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO FINAL OFFICE ACTION DATED JUNE 24, 2019

Dear Commissioner:

Applicant hereby submits a response to the Final Office Action dated June 24, 2019.

Applicant respectfully requests reconsideration and allowance of the pending claims.

The response is submitted with a petition to obtain a one-month extension of time, extending the deadline for responding to Oct 24, 2019. The Commissioner is hereby authorized to charge any fees associated with the filing of this response to Deposit Account No. 23-2415, referencing Docket No. 43060-707.304.

Prior to reconsidering this application on the merits, please amend the application as follows:

Amendments to the Claims begin on page 2.

Remarks begin on page 6.

The **Conclusion** is on page 8.

Amendments to the Claims

This listing of claims will replace all prior versions, amendments and listings of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicant reserves the right to pursue the subject matter of the withdrawn claims in this or any other appropriate patent application.

Listing of the Claims:

1. (Currently Amended) A stable oral liquid formulation, comprising:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate;

(iii) about 1 mg/ml a preservative, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

2. (Previously Presented) The stable oral liquid formulation of claim 1 further comprising a sweetener.

3. (Previously Presented) The stable oral liquid formulation of claim 2, wherein the sweetener is sucralose.

4. (Previously Presented) The stable oral liquid formulation of claim 1 further comprising a flavoring agent.

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5. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
6. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
7. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the buffer comprises about 0.8 to about 3.5 mg/ml citric acid.
8. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the buffer comprises about 0.1 to about 0.8 mg/ml sodium citrate.
9. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is less than about 3.5.
10. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.
11. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is about 3.3.
12. (Canceled)
13. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the preservative is sodium benzoate.
14. (Canceled)
15. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 18 months.
16. (Previously Presented) The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 24 months.
17. (Currently Amended) A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate;

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(iii) ~~about 1 mg/ml a preservative, wherein the preservative is selected from ascorbic acid, ascorbyl palmitate, BHA, BHT, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, methylparaben, ethylparaben, propylparaben, butylparaben, benzoic acid, sodium benzoate, potassium sorbate, and vanillin; and~~

(iv) water;

wherein the formulation is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

18. (Canceled)

19. (Currently Amended) The stable oral liquid formulation of claim ~~[[18]]31~~ further comprising a sweetener.

20. (Previously Presented) The stable oral liquid formulation of claim 19, wherein the sweetener is sucralose.

21. (Currently Amended) The stable oral liquid formulation of claim ~~[[18]]31~~ further comprising a flavoring agent.

22. (Currently Amended) The stable oral liquid formulation of claim ~~[[18]]31~~, wherein the formulation does not contain mannitol.

23. (Currently Amended) The stable oral liquid formulation of claim ~~[[18]]31~~, wherein the formulation does not contain silicon dioxide.

24. (Currently Amended) The stable oral liquid formulation of claim ~~[[18]]31~~, wherein the pH of the stable oral liquid formulation is less than about 3.5.

25. (Currently Amended) The stable oral liquid formulation of claim ~~[[18]]31~~, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.

26. (Currently Amended) The stable oral liquid formulation of claim ~~[[18]]31~~, wherein the pH of the stable oral liquid formulation is about 3.3.

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Response to the Final Office Action dated June 24, 2019

Attorney Docket No.: 43060-707.304

27. (Canceled)

28. (Currently Amended) The stable oral liquid formulation of claim [[18]]31, wherein the preservative is sodium benzoate.

29. (Currently Amended) The stable oral liquid formulation of claim [[18]]31, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 18 months.

30. (Currently Amended) The stable oral liquid formulation of claim [[18]]31, wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 24 months.

31. (New) A stable oral liquid formulation, comprising:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate;

(iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens; and

(iv) water;

wherein the formulation is stable at about $5 \pm 3^{\circ} \text{C}$ for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

Electronically Filed: October 24, 2019

Attorney Docket No.: 43060-707.304

REMARKS

Applicant would like to thank the Office for the Advisory Action dated September 16, 2019.

Claims 1-11, 13, 15-26, and 28-30 are pending in this application. By way of this response, claims 1, 17, 19, 21-26, and 28-30 have been amended, and claims 14 and 18 have been canceled. Claim 31 is newly added. Thus, claims 1-11, 13, 15-17, 19-26, and 28-31 under examination.

Support for the amendments can be found throughout the specifications and the originally filed claims, for example, paragraphs [0033], [0050], and [0054], Example E, and Table E-1. No new matter is presented by way of the amendments.

Withdrawal of any subject matter herein does not constitute an admission that the subject matter is unpatentable for any reason and Applicant reserves the right to file claims directed to withdrawn subject matter in this or a related application.

Rejection Under 35 U.S.C. §112(a)

Claims 1-11, 13, 15-26, and 28-30 are rejected under 35 U.S.C. § 112(a) as failing to comply with the written description requirement. Specifically, the Office noted that “while the claims limit the amount of enalapril, the buffer and the preservative are present in the formulations in any amount.”

Without acquiescing to the Office’s rejection but solely in an effort to expedite prosecution, claims 1 and 17 have been amended to recite “(ii) a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate; (iii) about 1 mg/ml sodium benzoate.”

The support for “about 1-4 mg/ml of a mixture of citric acid and sodium citrate” can be found, e.g., in Example E and Table E-1 of the specification. Indeed, the Office has acknowledged, in the Final Office Action dated June 24, 2019, that “Table E-1 (page 43) is directed toward liquid formulations comprising ... a buffer comprising 1 to 4 mg/mL of a mixture of citric acid and sodium citrate.” The support for “about 1 mg/ml sodium benzoate” can be found, e.g., paragraph [0050] of the specification.

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Response to the Final Office Action dated June 24, 2019

Attorney Docket No.: 43060-707.304

Newly added claim 31 recites “(ii) a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate; (iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens.” The support for “about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens” can be found, e.g., paragraph [0054] of the specification. The support for “about 1-4 mg/ml of a mixture of citric acid and sodium citrate” can be found, e.g., in Example E and Table E-1 of the specification as mentioned above.

Accordingly, Applicant respectfully requests the rejections be withdrawn.

Double Patenting Objection

Claims 1-11, 13, 15-26, and 28-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,669,008, claims 1-30 of U.S. Patent No. 9,808,442, claims 1-20 of U.S. Patent No. 10,039,745, and claims 1-30 of U.S. Patent No. 10,154,987.

Without acquiescing in this ground of rejection and solely in an effort to expedite prosecution, Applicant has submitted Terminal Disclaimers on August 1, 2019, with respect to U.S. Patent No. 9,669,008, U.S. Patent No. 9,808,442, U.S. Patent No. 10,039,745, and U.S. Patent No. 10,154,987, as well as U.S. Appl. Ser. No. 16/242,898.

The above submitted Terminal Disclaimers were approved on August 1, 2019.

The Terminal Disclaimers obviate the present rejections. Accordingly, Applicant respectfully requests that the rejections be withdrawn.

In view of the remarks and amendments submitted herein, Applicant believes that the Application is in condition for allowance and such action is earnestly solicited.

* * *

U.S. Patent Application No. 16/177,159

Attorney Docket No.: 43060-707.304

Response to the Final Office Action dated June 24, 2019

CONCLUSION

Applicant submits that this response fully addresses the Office Action mailed on June 24, 2019. Applicant believes that for the reasons set forth herein the pending claims are in condition for allowance and early and favorable consideration is respectfully requested.

Should the Examiner have any questions or concerns, the Examiner is encouraged to contact the undersigned attorney at (617) 598-7823.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: October 24, 2019

By: /Clark Lin/

Clark Y. Lin, Ph.D., Esq.

Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2306
Customer No. 021971

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	10/31/2018	Gerold L. Mosher	43060-707.304	3572
<div> <div>21971</div> <div>7590</div> <div>01/07/2020</div> <div>WILSON, SONSINI, GOODRICH & ROSATI</div> <div>650 PAGE MILL ROAD</div> <div>PALO ALTO, CA 94304-1050</div> </div>			<div>EXAMINER</div> <div>SPRINGER, STEPHANIE K</div>	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			01/07/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary**Application No.**

16/177,159

Applicant(s)

Mosher et al.

Examiner

STEPHANIE K SPRINGER

Art Unit

1629

AIA (FITF) Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 24 October 2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a) ☐ This action is **FINAL**.

2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1-11,13,15-17,19-26 and 28-31 is/are pending in the application.

5a) Of the above claim(s) ____ is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1-11,13,15-17,19-26 and 28-31 is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date ____.

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: ____.

Paper No(s)/Mail Date 4 pgs, 9/3/19.

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DETAILED ACTION

Continued Examination Under § 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 24, 2019 has been entered.

Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

This application is a continuation of application 16/003,994, now US Patent 10,154,987, filed on June 8, 2018, which is a continuation of application 15/802,341, now US Patent 10,039,745, filed on November 2, 2017, which is a continuation of application 15/613,622, now US Patent 9,808,442, filed on June 5, 2017, which is a continuation of application 15/081,603, now US Patent 9,669,008, filed on March 25, 2016 and claims priority to US provisional application 62/310,198, filed on March 18, 2016.

This application was granted Track One status on December 14, 2018.

Applicant's amendments filed October 24, 2019 amending claims 1, 17, 19, 21-26, and 28-30, canceling claims 12, 14, 18, and 27, and adding new claim 31 are acknowledged.

Applicant's arguments, filed October 24, 2019, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn.

Claims 1-11, 13, 15-17, 19-26, and 28-31 are pending and are the subject of the Office Action below.

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Previous Rejections Withdrawn

Any rejection not reiterated in the instant Office action is considered withdrawn. Certain new rejections are provided in the Office action below. Where Applicants arguments addressing the previous grounds of rejection relate to the present grounds of rejection, the Examiner addresses the Applicants comments.

Terminal Disclaimer

The terminal disclaimer filed on August 1, 2019 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patents 9,669,008; 9,808,442; 10,039,745; and 10,154,987 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on September 3, 2019 has been considered by the examiner. The submission is in compliance with the provisions of 37 CFR §§ 1.97 and 1.98. Enclosed with this Office Action is a return-copy of the Forms PTO-1449 with the examiner's initials and signature indicating those references that have been considered.

New Grounds of Rejection

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-11, 13, 15-17, 19-26, and 28-31 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 1-11, 15-17, 13, 15-17, 19-26, and 28-31 are indefinite for reciting the term “stable” because one of ordinary skill in the art could not reasonably determine the metes and bounds of this limitation. The term “stable” is not a term of the art such that the ordinarily skilled artisan would recognize what qualities or properties are encompassed therein. The term “stable” is a relative term which is not defined by the claims or the specification in a manner such that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One would reasonably recognize that a “stable” composition and stability refer to a degree of change or variability over a period of time; however, there is no clear disclosure such that one would recognize what types of changes are required to be “stable” such that one would recognize the metes and bounds of the instantly claimed invention. While the claims recite “the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period”, it is unclear if this is the only requirement of a “stable” composition or if other changes or variance would be tolerated while still meeting the instant requirements of stability. For example, while the formulation may still comprise “about 95% w/w or greater of the initial enalapril amount” it is unclear if this would also require the maintenance of a constant pH, *i.e.*, a stable pH, throughout this timeframe. Similarly, the formulation could comprise the requisite amount of enalapril, but it is unclear if enalapril which is not in solution would also meet the requirements. Note that the “related substances” falling within the scope of the “about 5% w/w or less total impurity or related substances” is not clearly defined such that one would recognize what “related substances” would render a composition unstable. The claims fail to clearly, precisely, or deliberately set forth how stability is measured and what standard or threshold value would be used to make such a

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comparison to determine whether the stability meets Applicant's claimed limitation. Absent this information, the claim clearly fails to set forth the metes and bounds of the subject matter for which Applicant is presently seeking protection.

Claims 1, 17, and 31, and all claims dependent therefrom, are indefinite because it is unclear if the recitations "wherein the formulation is stable at about 5 ± 3 °C for at least 12 months" and "wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period" are claim limitations. The ordinarily skilled artisan would not be able to reasonably determine how this limitation affects the scope of the claimed composition. It is unclear if additional components or elements are required in order to achieve the recited properties, or if the recitations merely describe a property that would necessarily result from the composition as claimed. In particular, it is unclear if the recited formulations would necessarily possess the properties "wherein the formulation is stable at about 5 ± 3 °C for at least 12 months" and "wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period". In other words, it is unclear if the recitations are claim limitations, or if the recitations regarding stability merely describe the composition of instant claims 1, 17, and 31. For example, it is unclear if the composition of instant claim 1 is capable of achieving stability at about 5 ± 3 °C for at least 12 months as recited, *i.e.*, would any composition comprising about 0.6 to about 1.2 mg/mL enalapril, about 1-4 mg/mL of a mixture of citric acid and sodium citrate, and about 1 mg/mL sodium benzoate in water necessarily achieve the recited stability, or if further components required in order to meet the recited limitations regarding stability. While the Examiner acknowledges that the term "comprising" in instant claims 1 and 31 is open ended, and allows for additional excipients, it is unclear if additional excipients are required in order to achieve the recited stability. Thus, it is unclear if the recitations are merely descriptive language to describe a property which is inherent to the formulations as claimed.

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Regarding the use of functional descriptive language, the Applicant's attention is directed towards MPEP § 2173.05(g): "the use of functional language in a claim may fail 'to provide a clear-cut indication of the scope of the subject matter embraced by the claim' and thus be indefinite. *In re Swinehart*, 439 F.2d 210, 213 (CCPA 1971). For example, when claims merely recite a description of a problem to be solved *or a function or result achieved by the invention*, the boundaries of the claim scope may be unclear. *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d1244, 1255 (Fed. Cir. 2008) (noting that the Supreme Court explained that a vice of functional claiming occurs 'when the inventor is painstaking when he recites what has already been seen, and then uses conveniently functional language at the exact point of novelty')". Examiners should consider the following factors when examining claims that contain functional language to determine whether the language is ambiguous: (1) whether there is a clear cut indication of the scope of the subject matter covered by the claim; (2) whether the language sets forth well-defined boundaries of the invention or only states a problem solved *or a result obtained*; and (3) whether one of ordinary skill in the art would know from the claim terms what structure or steps are encompassed by the claim. In the instant case, it is unclear whether the language sets forth well-defined boundaries of the invention or only states a result obtained.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are thus rejected.

New Grounds of Rejections

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), first paragraph:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13, 15-17, 19-26, and 28-31 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. See MPEP § 706.03(o).

In particular, the specification fails to provide adequate support for the limitations wherein the composition “a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate” as recited in instant claims 1, 17, and 31. See MPEP § 2163.06 (I) and *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

In the amendment filed October 24, 2019, Applicant amended independent claims 1 and 17 and added new claim 31 to recite the limitation, “a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate”.

Applicants allege that support for the limitations wherein the amount is “about 1-4 mg/ml of a mixture of citric acid and sodium citrate” may be found in throughout the specifications and the originally filed claims; Applicant particularly cites to paragraphs 33, 50, and 54, and Example E and Table E-1 at page 43 of the original specification as filed. Applicant asserts, “No new matter is presented by way of the amendments.”

Upon analysis of the originally filed disclosure, the Examiner is unable to find support for the limitation “a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate”. Turning to paragraph 67, the specification recites, “In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation”. At paragraph 71, the specification states,

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“In some embodiments, sodium citrate dehydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation”. While Applicants have *specific* working examples, such working examples are limited to *specific* formulations comprising *specific* amounts of citric acid and sodium citrate, in a specific ratio.

As Applicant notes at page 6 of the remarks filed October 24, 2019, the Examiner summarized Example E thusly:

Table E-1 (page 43) is directed towards liquid formulations comprising

- (i) 1.0 mg/ml enalapril maleate;
- (ii) a buffer comprising 1 to 4 mg/mL of a mixture of citric acid and sodium citrate;
- (iii) 1 mg/mL sodium benzoate; and
- (iv) water.

The Examiner notes that the Examiner’s summarization of the compositions of Example E does not provide support for the amendments. More specifically, turning towards Example E, one sees that the amounts of citric acid and sodium citrate are recited in particular amounts, not in a range. Examples E1-E4 each comprise 3.29 mg/mL citric acid and 0.75 mg/mL sodium citrate; Example E5 comprises 1.65 mg/mL citric acid and 0.38 mg/mL sodium citrate; and Example E6 comprises 0.82 mg/mL citric acid and 0.19 mg/mL sodium citrate. These six examples support a specific buffer comprising a specific ratio of citric acid to sodium citrate, in specific amounts, and do not provide support for the recited range of “about 1-4 mg/ml of a mixture of citric acid and sodium citrate”.

Thus, the limitation “a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate” is considered new matter because nowhere in the originally filed disclosure do Applicants disclose the use of the combination of citric acid and sodium citrate in this range, nor does Applicant disclose the use of said combination in any and all ratios falling within the scope of the recited range.

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For these reasons, it appears that the requirement that the composition comprises “about 1-4 mg/ml of a mixture of citric acid and sodium citrate” wherein the citric acid and sodium citrate are in any combination was not particularly contemplated at the time of the invention. Accordingly, the amendments are considered new matter and are properly rejected under 35 U.S.C. 112, first paragraph.

Conclusion

No claims are allowed in this application.

If applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported *in ipsi verbis*, clarification on the record may be helpful). Should applicants present new claims, applicants should clearly identify where support can be found in the disclosure.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Springer whose telephone number is 571-270-7380. The examiner can normally be reached on Monday through Thursday from 8 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren, can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-270-8380.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stephanie Springer/
Examiner, Art Unit 1629

/JEFFREY S LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	10/31/2018	Gerold L. Mosher	43060-707.304	3572
<div> <div>21971</div> <div>7590</div> <div>03/06/2020</div> <div>WILSON, SONSINI, GOODRICH & ROSATI</div> <div>650 PAGE MILL ROAD</div> <div>PALO ALTO, CA 94304-1050</div> </div>			<div>EXAMINER</div> <div>SPRINGER, STEPHANIE K</div>	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			03/06/2020	ELECTRONIC

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The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

<i>Applicant-Initiated Interview Summary</i>	Application No. 16/177,159		Applicant(s) Mosher et al.	
	Examiner STEPHANIE K SPRINGER		Art Unit 1629	AIA (FITF) Status Yes

All participants (applicant, applicants representative, PTO personnel):

(1) STEPHANIE K. SPRINGER. (3) ____.

(2) Clark Lin. (4) ____.

Date of Interview: 28 February 2020.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: ____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1.

Identification of prior art discussed: ____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed rejections of record. Examiner suggested presenting additional evidence supporting the breadth of the instantly claimed invention.

No agreement was reached..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Stephanie K Springer/ Examiner, Art Unit 1629	/JEFFREY S LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629
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Summary of Record of Interview Requirements**Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record**

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews

Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 3572
Serial No.: 16/177,159	Examiner: SPRINGER, Stephanie K.
Filed: October 31, 2018	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on May 15, 2020, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u> /Paula Derby/ </u></p> <p align="right">Paula Derby</p>

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION DATED JANUARY 7, 2020

Dear Commissioner:

Applicant hereby submits a response to the Non-Final Office Action dated January 7, 2020 (the “Office Action”). Applicant respectfully requests reconsideration and allowance of the pending claims.

The response is submitted with a petition to obtain a two-month extension of time, extending the deadline for responding to June 7, 2020. The Commissioner is hereby authorized to charge any fees associated with the filing of this response to Deposit Account No. 23-2415, referencing Docket No. 43060-707.304.

Prior to reconsidering this application on the merits, please amend the application as follows:

Amendments to the Claims begin on page 2.

Remarks begin on page 7.

The **Conclusion** is on page 11.

Amendments to the Claims

This listing of claims will replace all prior versions, amendments and listings of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicant reserves the right to pursue the subject matter of the withdrawn claims in this or any other appropriate patent application.

Listing of the Claims:

1. (Currently amended) An ~~stable~~ oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising ~~about 1-4 mg/ml of~~ a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
 - (iii) about 1 mg/ml sodium benzoate; and
 - (iv) water;

wherein the formulation maintains ~~is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 12 months; and~~

~~wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of a the given storage period of at least 12 months at about $5 \pm 3^{\circ}\text{C}$.~~
2. (Currently amended) The ~~stable~~ oral liquid formulation of claim 1 further comprising a sweetener.
3. (Currently amended) The ~~stable~~ oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. (Currently amended) The ~~stable~~ oral liquid formulation of claim 1 further comprising a flavoring agent.
5. (Currently amended) The ~~stable~~ oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.

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6. (Currently amended) The ~~stable~~-oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
7. (Currently amended) The ~~stable~~-oral liquid formulation of claim 1, wherein the buffer comprises about 0.8 to about 3.5 mg/ml citric acid.
8. (Currently amended) The ~~stable~~-oral liquid formulation of claim 1, wherein the buffer comprises about 0.1 to about 0.8 mg/ml sodium citrate.
9. (Currently amended) The ~~stable~~-oral liquid formulation of claim 1, wherein the pH of the ~~stable~~-oral liquid formulation is less than about 3.5.
10. (Currently amended) The ~~stable~~-oral liquid formulation of claim 1, wherein the pH of the ~~stable~~-oral liquid formulation is between about 3 and about 3.5.
11. (Currently amended) The ~~stable~~-oral liquid formulation of claim 1, wherein the pH of the ~~stable~~-oral liquid formulation is about 3.3.
12. (Canceled)
13. (Currently amended) The ~~stable~~-oral liquid formulation of claim 1, wherein the preservative is sodium benzoate.
14. (Canceled)
15. (Currently amended) The ~~stable~~-oral liquid formulation of claim 1, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months ~~is stable at about 5 ± 3° C for at least 18 months.~~
16. (Canceled)
17. (Currently amended) An ~~stable~~-oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising ~~about 1-4 mg/ml of~~ a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
 - (iii) about 1 mg/ml sodium benzoate; ~~and~~

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Response to the Non-Final Office Action dated January 7, 2020(iv) water; and(v) optionally a sweetener, a flavoring agent, or both;wherein the formulation maintains ~~is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 12 months;~~~~and~~~~wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of a the given storage period~~ of at least 12 months at about $5 \pm 3^{\circ}\text{C}$.

18. (Canceled)

19. (Currently amended) The ~~stable~~-oral liquid formulation of claim 31 further comprising a sweetener.20. (Currently amended) The ~~stable~~-oral liquid formulation of claim 19, wherein the sweetener is sucralose.21. (Currently amended) The ~~stable~~-oral liquid formulation of claim 31 further comprising a flavoring agent.22. (Currently amended) The ~~stable~~-oral liquid formulation of claim 31, wherein the formulation does not contain mannitol.23. (Currently amended) The ~~stable~~-oral liquid formulation of claim 31, wherein the formulation does not contain silicon dioxide.24. (Currently amended) The ~~stable~~-oral liquid formulation of claim 31, wherein the pH of the ~~stable~~-oral liquid formulation is less than about 3.5.25. (Currently amended) The ~~stable~~-oral liquid formulation of claim 31, wherein the pH of the ~~stable~~-oral liquid formulation is between about 3 and about 3.5.26. (Currently amended) The ~~stable~~-oral liquid formulation of claim 31, wherein the pH of the ~~stable~~-oral liquid formulation is about 3.3.

27. (Canceled)

28. (Currently amended) The ~~stable~~-oral liquid formulation of claim 31, wherein the preservative is sodium benzoate.
29. (Currently amended) The ~~stable~~-oral liquid formulation of claim 31, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months ~~is stable at about $5 \pm 3^\circ \text{C}$ for at least 18 months~~.
30. (Canceled)
31. (Currently amended) An ~~stable~~-oral liquid formulation, comprising:
- (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising ~~about 1-4 mg/ml of~~ a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
 - (iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens; and
 - (iv) water;
- wherein the formulation maintains ~~is stable at about $5 \pm 3^\circ \text{C}$ for at least 12 months~~;
- ~~and~~
- ~~wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of a the given storage period of at least 12 months at about $5 \pm 3^\circ \text{C}$.~~
32. (New) The oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.
33. (New) The oral liquid formulation of claim 1, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.
34. (New) The oral liquid formulation of claim 1, wherein the buffer is present at a concentration of about 10 mM in the oral liquid formulation.

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35. (New) The oral liquid formulation of claim 31, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.
36. (New) The oral liquid formulation of claim 31, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

* * *

REMARKS

Claims 1-11, 13, 15-17, 19-26, and 28-31 were pending in this application.

By way of this response, claims 1-11, 13, 15, 17, 19-26, 28, 29, and 31 have been amended, and claims 16 and 30 are canceled. New claims 32-36 are added. Support for the amendments can be found throughout the specifications and the originally filed claims, for example, paragraphs [0038], [0039], [0066], and [0076], Example B, Example E, Table B-1, Table B-2, Table E-1, and Table E-2 of the instant application published as US 2019/0070147 A1. No new matter is presented by way of the amendments.

Upon entry of the amendments, claims 1-11, 13, 15, 17, 19-26, 28, 29, and 31-36 are pending and under examination.

Withdrawal of any subject matter herein does not constitute an admission that the subject matter is unpatentable for any reason and Applicant reserves the right to file claims directed to withdrawn subject matter in this or a related application.

Interview Summary (Interview of February 28, 2020)

Applicant expresses its appreciation to Examiner Springer for conducting a telephone interview with Applicant's representative, Clark Lin, and for offering suggestions of overcoming the outstanding rejections. During the interview, the rejections of record were discussed, and it was suggested to the Applicant to present additional evidence supporting the pending claims.

Rejection Under 35 U.S.C. §112(b)

Claims 1-11, 13, 15-17, 19-26, and 28-31 were rejected under 35 U.S.C. § 112(b) as allegedly indefinite for reciting the term "stable."

Without acquiescing to the Office's rejection, Applicant submits that the amended claims 1-11, 13, 15-17, 19-26, and 28-31 do not recite the term "stable," rendering the rejection moot. Therefore, Applicant respectfully requests the rejection be withdrawn.

Rejection Under 35 U.S.C. §112(a)

Claims 1-11, 13, 15-17, 19-26, and 28-31 were rejected under 35 U.S.C. § 112(a) as allegedly failing to comply with the written description requirement. Specifically, the Office remarks that the specification fails to provide adequate support for claim limitations reciting “a buffer comprising about 1-4 mg/ml of a mixture of citric acid and sodium citrate” in the independent claims.

Without acquiescing to the Office’s rejection, Applicant submits that the amended independent claims 1, 17 and 31 recite, in part, “wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation.” A buffer concentration “between about 5 mM and about 20 mM” was described in the instant application, published as US 2019/0070147 A1, e.g., in paragraph [0066], Example B, Example E, Table B-1, Table B-2, Table E-1.

Applicant further submits an Inventor Declaration by Dr. Gerold Mosher dated May, 14, 2020 (the “Mosher Declaration”), with evidence to overcome the §112(a) rejection asserted by the Office. In the Mosher Declaration, Dr. Mosher explains that:

The '159 application describes that stable oral enalapril liquid formulations can be prepared with suitable buffers including citrate buffers at varying concentrations. Formulations containing a mixture of citric acid and sodium citrate at various amounts as buffers are exemplified in the '159 application, for example, formulations B1-B3 in Example B and formulations E1-E6 in Example E. The buffer concentrations of formulations E1 to E6 are the following:

Buffer Concentration	E1	E2	E3	E4	E5	E6
Citric acid (mg/mL)	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate (mg/mL)	0.75	0.75	0.75	0.75	0.38	0.19
Citrate concentration (mM)	20	20	20	20	10	5

Mosher Declaration, ¶13.

In addition, Dr. Mosher provided additional embodiments of the citrate buffer-based formulations in the Mosher Declaration as “exemplary formulations H1 and H7-H13 presented below in Table 1, which all contain a mixture of citric acid and sodium citrate”. See, Mosher

Declaration, ¶15. According to the storage stability results illustrated in Table 2 and Table 3 (not reproduced here), formulations of Table 1 demonstrated excellent stability. *See*, Mosher Declaration, ¶17-18, Table 2, and Table 3.

Table 1

Ingredients	Compositions (mg/mL) for Stability Testing							
	H1 Citrate	H7 Citrate	H8 Citrate	H9 Citrate	H10 Citrate	H11 Citrate	H12 Citrate	H13 Citrate
Citric acid, anhydrous	1.82	1.92	1.92	1.92	1.92	1.92	3.84	3.84
Sodium citrate, dihydrate	0.15	-	-	-				
Citrate concentration (mM)	10	10	10	10	10	10	20	20
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose NF	0.70	0.70	0.70	0.70				
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	qs	qs	qs	qs	qs	qs	qs	qs
pH	3.3	3.3	4.0	4.5	3	4	3	4

Dr. Mosher explains: “Table E-2 and Tables 1-3 show that formulations of the ’159 application can be prepared using a mixture of citric acid and sodium citrate, and the amount of the total citrate can vary, at least between about 5 mM and about 20 mM. All the formulations in Table E-2 and Tables 1-3 demonstrated superior stability, e.g., retaining greater than about 98% of the initial enalapril maleate content and having less than about 2% w/w total impurity after 52 weeks at 5 °C.” Mosher Declaration, ¶19.

Dr. Mosher further remarks that “although formulations exemplified in the ’159 application and in Tables 1-3 have a total citrate amount of about 5 mM, 10 mM or 20 mM, I would expect that similar formulations having a total citrate amount between about 5 mM and about 20 mM to have similar, superior stability as the exemplified formulations.” Mosher Declaration, ¶20.

Thus, Applicant submits a person of ordinary skill in the art reading the present disclosure, for example, paragraph [0066] and Examples B and E, would appreciate that the disclosed formulations can be prepared with a mixture of citric acid and sodium citrate as a

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buffer at a concentration of at least between about 5 mM and about 20 mM. Therefore, the amended claims are supported for written description purposes in the instant application.

Accordingly, Applicant respectfully requests reconsideration and allowance of the pending claims.

* * *

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CONCLUSION

Applicant submits that this response fully addresses the Non-Final Office Action mailed on January 7, 2020. Applicant believes that for the reasons set forth herein the pending claims are in condition for allowance and early and favorable consideration is respectfully requested.

Should the Examiner have any questions or concerns, the Examiner is encouraged to contact the undersigned attorney at (617) 598-7823.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: May 15, 2020

By: /Clark Lin/
Clark Y. Lin, Ph.D., Esq.
Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2306
Customer No. 021971

Attorney Docket No. 43060-707.304

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 3572
Serial No.: 16/177,159	Examiner: SPRINGER, Stephanie K
Filed: October 31, 2018	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on May 15, 2020, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u>/Paula Derby/</u></p>

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132

I, **Gerold Mosher**, state and declare as follows:

1. I am currently employed at Azurity Pharmaceuticals, Inc., a company formed in May 2019 by the acquisition of Silvergate Pharmaceuticals, Inc. by CutisPharma, Inc.
2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.
3. I have been employed at Silvergate Pharmaceuticals and now Azurity Pharmaceuticals since 2013, and my current position is Vice President of Product Development. As part of my job duties, I develop oral formulations for pediatric use. I have a small laboratory where I

develop, characterize and move formulations through the steps required for FDA approval and eventual sale.

4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also been employed by small startup companies to develop new solubilizing technology for oral, injectable, and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for about 40 years, and have extensive experience in developing pharmaceutical formulations. My *Curriculum Vitae* is attached as Exhibit A.

6. I am familiar with the subject matter claimed in U.S. Pat. App. Ser. No. 16/177,159 (“the ’159 application”), and I am a named inventor on this application. Silvergate Pharmaceuticals, Inc. is the assignee of all rights in the invention of the pending ’159 application.

7. I am aware of the Non-Final Office Action mailed in this matter on January 7, 2020. I am also aware that the pending claims were rejected under 35 U.S.C. 112(b) and 35 U.S.C. 112(a).

8. I am submitting this declaration to address some of the comments made in the Office Action,.

9. The ’159 application relates to enalapril oral liquid formulations that are stable at about 5 ± 3 °C for at least 12 months. The development of this described enalapril formulation was oriented on preparing a safe, stable, uniform oral liquid with minimal degradation and having an acceptable taste for pediatric patients.

10. Traditionally, approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in “Nahata” and subsequently administering the suspension to the patient, or (3) reconstituting a powder in a liquid carrier. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty swallowing solid oral dosage forms. For the second method,

extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination.

11. Compared to these currently available methods, the enalapril oral liquid formulation claimed in the '159 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

12. The oral enalapril liquid formulations of the '159 application have superior stability—they are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

13. The '159 application describes that stable oral enalapril liquid formulations can be prepared with suitable buffers including citrate buffers at varying concentrations. Formulations containing a mixture of citric acid and sodium citrate at various amounts as buffers are exemplified in the '159 application, for example, formulations B1-B3 in Example B and formulations E1-E6 in Example E. The buffer concentrations of formulations E1 to E6 are the following:

Buffer Concentration	E1	E2	E3	E4	E5	E6
----------------------	----	----	----	----	----	----

Citric acid (mg/mL)	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate (mg/mL)	0.75	0.75	0.75	0.75	0.38	0.19
Citrate concentration (mM)	20	20	20	20	10	5

14. The storage stability of formulations E1-E6 is summarized in Table E-2, partially copied below for the stability results at 5 °C. After storing at about 5 °C for a period of 52 or 62 weeks, the combined amount of two primary degradants, Enalaprilat and diketopiperazine, remained less than 1 % w/w, demonstrating excellent formulation stability. As shown in Table E-2, the formulations prepared with 5 mM, 10 mM or 20 mM of a mixture of citric acid and sodium citrate as a buffer have comparable stability over 52 weeks at about 5 °C.

TABLE E-2								
Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	°C	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		

15. Further evidence of the superior stability of the citrate buffer-based formulations disclosed in the '159 application can be found in exemplary formulations H1 and H7-H13 presented below in Table 1, which all contain a mixture of citric acid and sodium citrate.

16. Formulations H1 and H7-H13 were prepared according to the compositions in Table 1 and titrated if needed to the target pH with 5N hydrochloric acid or 5N sodium hydroxide. Formulations H1 and H7-H9 were placed into HDPE containers and sealed with screw caps and induction sealing and stored at 5 °C. Formulations H10-H13 were placed into glass containers, sealed with Teflon lined screw caps and stored at 60 °C. The formulations were sampled at various

times during storage. Samples were analyzed by HPLC for enalapril maleate and enalapril related substances. The results of the analyses are presented in Table 2 and Table 3.

17. The enalapril maleate assay results in Table 2 show that formulations H1 and H7-H9 retain greater than 98% of the initial enalapril maleate content and have less than 2% of total impurity after 52 weeks at 5 °C. Formulations H1 and H7-H9 demonstrated excellent stability. Further, by comparing the amounts of the two primary degradants (i.e., Diketopiperazine and Enalaprilat) in Table 2 and Table E-2, it can be expected that formulations E1-E6 have comparable stability to formulations H1 and H7-H9.

18. In Table 3, the stability of formulations prepared with a mixture of citric acid and sodium citrate as a buffer at two different concentrations and pH values were compared under an accelerated condition at 60 °C. The results in Table 3 show that a citrate buffer concentration of about 10 mM or 20 mM, at least when adjusted to a pH value of about 3-4, are suitable to be used in formulations of the '159 application and yield similar stability.

Table 1

Compositions (mg/mL) for Stability Testing								
Ingredients	H1 Citrate	H7 Citrate	H8 Citrate	H9 Citrate	H10 Citrate	H11 Citrate	H12 Citrate	H13 Citrate
Citric acid, anhydrous	1.82	1.92	1.92	1.92	1.92	1.92	3.84	3.84
Sodium citrate, dihydrate	0.15	-	-	-				
Citrate concentration (mM)	10	10	10	10	10	10	20	20
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose NF	0.70	0.70	0.70	0.70				
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	qs	qs	qs	qs	qs	qs	qs	qs
pH	3.3	3.3	4.0	4.5	3	4	3	4

Table 2

Assay and Total Degradant Content After Storage						
	Storage		Formulation			
	°C	Weeks	H1	H7	H8	H9
Enalapril Maleate (% initial)	5	0	100.0	100.0	100.0	100.0
		2	100.1	100.7	100.4	100.3
		4	100.2	99.8	100.0	99.6
		8	100.0	99.6	100.9	100.7

		24	99.8	100.4	100.1	99.8
		28	99.8	99.7	-	-
		36	-	-	99.9	99.4
		52	99.9	99.8	99.5	99.2
Diketopiperazine (% w/w of enalapril maleate)	5	0	<0.05	<0.05	<0.05	<0.05
		2	<0.05	<0.05	<0.05	<0.05
		4	<0.05	<0.05	<0.05	<0.05
		8	<0.05	<0.05	<0.05	<0.05
		24	0.06	0.07	<0.05	<0.05
		28	0.09	0.10	-	-
		36	-	-	0.06	<0.05
		52	0.14	0.12	0.07	<0.05
Enalaprilat (% w/w of enalapril maleate)	5	0	<0.05	<0.05	0.09	0.10
		2	0.06	0.07	0.13	0.16
		4	0.08	0.08	0.17	0.24
		8	0.15	0.14	0.27	0.37
		24	0.19	0.20	0.41	0.58
		28	0.35	0.36	-	-
		36	-	-	0.85	1.17
		52	0.53	0.52	1.10	1.49
Total Impurities (% w/w of enalapril maleate)	5	0	<0.05	<0.05	0.09	0.10
		2	0.07	0.07	0.14	0.16
		4	0.09	0.10	0.20	0.26
		8	0.18	0.18	0.31	0.41
		24	0.25	0.27	0.43	0.60
		28	0.44	0.46	-	-
		36	-	-	0.91	1.20
		52	0.68	0.65	1.18	1.53

Table 3
Assay Results After Storage of Formulations at 60 °C

Buffer	mM	Enalapril Maleate, pH 3 (% initial)				Enalapril Maleate, pH 4 (% initial)			
		0 Days	2 Days	4 Days	7 Days	0 Days	2 Days	4 Days	7 Days
Citrate	10	100.0	97.1	97.2	95.5	100.0	97.2	96.6	94.6
	20	100.0	97.1	96.8	95.2	100.0	96.8	96.4	94.4

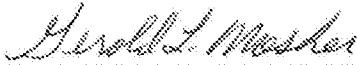
19. As presented above, Table E-2 and Tables 1-3 show that formulations of the '159 application can be prepared using a mixture of citric acid and sodium citrate, and the amount of the total citrate can vary, at least between about 5 mM and about 20 mM. All the formulations in Table E-2 and Tables 1-3 demonstrated superior stability, e.g., retaining greater than about 98% of the

initial enalapril maleate content and having less than about 2% w/w total impurity after 52 weeks at 5 °C.

20. Further, although formulations exemplified in the '159 application and in Tables 1-3 have a total citrate amount of about 5 mM, 10 mM or 20 mM, I would expect that similar formulations having a total citrate amount between about 5 mM and about 20 mM to have similar, superior stability as the exemplified formulations.

21. I declare that all statements made herein are true to the best of my knowledge, or if made upon information and belief, are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted on this 5th day of May, 2020



Gerold L. Mosher, Ph.D.

Attorney Docket No. 43060-707.304
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	MOSHER; Gerold L. et al.	Group Art Unit:	1629
Serial Number:	16/177,159	Examiner:	SPRINGER, Stephanie K.
Filing or 371 (c) Date:	2018-10-31	CONFIRMATION NO:	3572
Title:	ENALAPRIL FORMULATIONS		

FILED ELECTRONICALLY ON: June 5, 2020

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☐ *37 CFR § 1.97 (b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
-- OR --
 - ☐ (3) It is being filed before the mailing of a first Office action on the merits;
-- OR --
 - ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☒ *37 CFR § 1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97 (e) provided concurrently herewith;
-- OR --
 - ☒ a fee of \$240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR § 1.97 (d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
-- AND --
 - ii. a fee of \$240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☐ *37 CFR §1.97 (e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
-- AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☐ *Statement Under 37 C.F.R. §1.704(d)*. Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☒ *37 CFR §1.98 (a) (2)*. The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☐ *37 CFR §1.98(a)(3)*. The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
- OR --
- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☐ *37 CFR §1.98(d)*. Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$240.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.43060-707.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: June 5, 2020

By: /Clark Lin/
Clark Y. Lin, Reg. No. 67,024

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
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NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 07/16/2020
 WILSON, SONSINI, GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050

EXAMINER

RAO, SAVITHA M

ART UNIT

PAPER NUMBER

1629

DATE MAILED: 07/16/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	10/31/2018	Gerold L. Mosher	43060-707.304	3572

TITLE OF INVENTION: ENALAPRIL FORMULATIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	10/16/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

21971 7590 07/16/2020
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177.159	10/31/2018	Gerold L. Mosher	43060-707.304	3572

TITLE OF INVENTION: ENALAPRIL FORMULATIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	10/16/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	10/31/2018	Gerold L. Mosher	43060-707.304	3572
21971	7590	07/16/2020	EXAMINER	
WILSON, SONSINI, GOODRICH & ROSATI			RAO, SAVITHA M	
650 PAGE MILL ROAD			ART UNIT	
PALO ALTO, CA 94304-1050			PAPER NUMBER	
			1629	
DATE MAILED: 07/16/2020				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/177,159	Applicant(s) Mosher et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 05/15/2020.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are See Continuation Sheet. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov**.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. <input type="checkbox"/> Notice of References Cited (PTO-892) 2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>06/05/2020</u> . 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. <input checked="" type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date. <u>07/01/2020</u> .	5. <input type="checkbox"/> Examiner's Amendment/Comment 6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance 7. <input type="checkbox"/> Other _____.
--	--

/SAVITHA M RAO/
Primary Examiner, Art Unit 1629

Continuation Sheet (PTOL-37)

Application No. 16/177,159

Continuation of 3. The allowed claim(s) is/are: 1-11,13,15,17,19-29 and 31-36

Application/Control Number: 16/177,159
Art Unit: 1629

Page 2

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-11, 13, 15, 17, 19-29 and 31-36 are pending in the instant application.

Applicants representative Mr. Clark Lin interviewed with the examiner to discuss the claim amendments and the submitted affidavit on 7/1/2020. Please see the attached interview summary for details.

Information Disclosure Statement

The information disclosure statement (IDS) dated 06/05/2020 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Terminal disclaimer

The terminal disclaimer filed on 08/01/2019 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **US patents 9669008, 9808442, 10039745 and 10154987 and US application 16/242898** have been reviewed and is accepted. The terminal disclaimer has been recorded.

Rule 37 CFR 1.132 Declaration

Applicant's submission of the declarations of Gerold Mosher under 37 CFR 1.132 filed 05/15/2020 is acknowledged. The declarations is found to be persuasive in

Application/Control Number: 16/177,159

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Art Unit: 1629

overcoming the outstanding rejections set forth in the non-final rejection dated 01/07/2020.

REASONS FOR ALLOWANCE

In view of the applicants claim amendments, arguments and the declaration filed on 05/15/2020 and the following examiners statement of reasons for allowance, claims 1-11, 13, 15, 17, 19-29 and 31-36 are found to be allowable.

Following a diligent search it was determined that the prior art neither teaches nor provides adequate motivation to arrive at the instantly claimed oral liquid formulation, comprising: (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation; (iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens; and (iv) water; wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a the given storage period of at least 12 months at about 5 ± 30 C.

Conclusion

Claims 1-11, 13, 15, 17, 19-29 and 31-36 (renumbered 1-29) are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Application/Control Number: 16/177,159
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA M RAO/
Primary Examiner, Art Unit 1629

<i>Applicant-Initiated Interview Summary</i>	Application No. 16/177,159	Applicant(s) Mosher et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	AIA (FITF) Status Yes

All participants (applicant, applicants representative, PTO personnel):

(1) SAVITHA M. RAO. (3) ____.

(2) Clark Lin. (4) ____.

Date of Interview: 01 July 2020.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: ____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1.

Identification of prior art discussed: none.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicants discussed the claim amendments and how that overcomes the 112 rejection on file.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/SAVITHA M RAO/ Primary Examiner, Art Unit 1629	
--	--

Summary of Record of Interview Requirements**Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record**

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews

Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Electronically Filed On: July 22, 2020

PATENT

Attorney Docket No. 43060-707.304

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application)	Confirmation No.: 3572
)	
Inventors: Gerold L. Mosher, et al.)	Art Unit: 1629
)	
Application No.: 16/177,159)	Examiner: Rao, Savitha M.
)	
Filed: October 31, 2018)	Customer No. 021971
)	
Title: ENALAPRIL FORMULATIONS)	
)	
)	
)	

Mail Stop Amendment

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312

Dear Commissioner:

This Amendment under 37 C.F.R. § 1.312 is submitted after the Notice of Allowance mailed July 16, 2020. Entry of the following amendment under 37 C.F.R. § 1.312 is respectfully requested.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

Conclusion begins on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in this application. Applicant reserves the right to pursue any subject matter of any canceled claims in this or any other appropriate patent application. Support for these claims is provided in the remarks following the listing of claims.

Listing of the Claims

1. (Previously presented) An oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
 - (iii) about 1 mg/ml sodium benzoate; and
 - (iv) water;

wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5 \pm 3^\circ \text{C}$.
2. (Previously presented) The oral liquid formulation of claim 1 further comprising a sweetener.
3. (Previously presented) The oral liquid formulation of claim 2, wherein the sweetener is sucralose.
4. (Previously presented) The oral liquid formulation of claim 1 further comprising a flavoring agent.
5. (Previously presented) The oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
6. (Previously presented) The oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
7. (Previously presented) The oral liquid formulation of claim 1, wherein the buffer comprises about 0.8 to about 3.5 mg/ml citric acid.

Application No. 16/177,159

Amendment under § 1.312(a) filed on **July 22, 2020**

8. (Previously presented) The oral liquid formulation of claim 1, wherein the buffer comprises about 0.1 to about 0.8 mg/ml sodium citrate.
9. (Previously presented) The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is less than about 3.5.
10. (Previously presented) The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.
11. (Previously presented) The oral liquid formulation of claim 1, wherein the pH of the oral liquid formulation is about 3.3.
12. (Canceled)
13. (Canceled)
14. (Canceled)
15. (Previously presented) The oral liquid formulation of claim 1, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about $5 \pm 3^{\circ}$ C.
16. (Canceled)
17. (Previously presented) An oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
 - (iii) about 1 mg/ml sodium benzoate;
 - (iv) water; and
 - (v) optionally a sweetener, a flavoring agent, or both;wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5 \pm 3^{\circ}$ C.
18. (Canceled)

Application No. 16/177,159

Amendment under § 1.312(a) filed on **July 22, 2020**

19. (Previously presented) The oral liquid formulation of claim 31 further comprising a sweetener.
20. (Previously presented) The oral liquid formulation of claim 19, wherein the sweetener is sucralose.
21. (Previously presented) The oral liquid formulation of claim 31 further comprising a flavoring agent.
22. (Previously presented) The oral liquid formulation of claim 31, wherein the formulation does not contain mannitol.
23. (Previously presented) The oral liquid formulation of claim 31, wherein the formulation does not contain silicon dioxide.
24. (Previously presented) The oral liquid formulation of claim 31, wherein the pH of the oral liquid formulation is less than about 3.5.
25. (Previously presented) The oral liquid formulation of claim 31, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.
26. (Previously presented) The oral liquid formulation of claim 31, wherein the pH of the oral liquid formulation is about 3.3.
27. (Canceled)
28. (Canceled)
29. (Previously presented) The oral liquid formulation of claim 31, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about $5 \pm 3^{\circ} \text{C}$.
30. (Canceled)
31. (Previously presented) An oral liquid formulation, comprising:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

Application No. 16/177,159

Amendment under § 1.312(a) filed on **July 22, 2020**

(ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;

(iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens; and

(iv) water;

wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about $5 \pm 3^{\circ} \text{C}$.

32. (Previously presented) The oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.

33. (Previously presented) The oral liquid formulation of claim 1, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

34. (Previously presented) The oral liquid formulation of claim 1, wherein the buffer is present at a concentration of about 10 mM in the oral liquid formulation.

35. (Previously presented) The oral liquid formulation of claim 31, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.

36. (Previously presented) The oral liquid formulation of claim 31, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

* * *

Application No. 16/177,159
Amendment under § 1.312(a) filed on **July 22, 2020**

REMARKS

Amendment to the Claims

Applicant respectfully requests entrance of this Amendment to amend the claims of the instant application. After entry of this amendment, claims 1-11, 15, 17, 19-26, 29, and 31-36 are pending in this case. Claims 13 and 28, both of which recited “wherein the preservative is sodium benzoate”, have been canceled to eliminate redundancy. No other claims have been amended or added. Accordingly, Applicant respectfully submits that the amendment does not add any new matter or raise any new issues.

Summary of Applicant-Initiated Examiner Interview

Applicant also thanks Examiner Rao for the courtesy of a telephonic interview with Applicant’s representative Clark Y. Lin on July 1, 2020. During the interview rejections under 35 U.S.C. § 112 were discussed.

Application No. 16/177,159
Amendment under § 1.312(a) filed on **July 22, 2020**

CONCLUSION

Applicant believes that this application is in condition of allowance and requests expeditious issuance of the claims. Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned at (617) 598-7823. The Commissioner is authorized to charge any additional fees that may be required, including petition fees and extension of time fees, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No.: 43060-707.304).

Respectfully submitted,

Date: July 22, 2020

By: /Clark Lin/
Clark Lin, Esq., Reg. No. 67,024

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone: (650) 493-9300
Client No. 021971

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

21971 7590 07/16/2020
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Erin Dugan	(Typed or printed name)
/erin dugan/	(Signature)
July 23, 2020	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	10/31/2018	Gerold L. Mosher	43060-707.304	3572

TITLE OF INVENTION: ENALAPRIL FORMULATIONS

APPL. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	10/16/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

Wilson, Sonsini, Goodrich & Rosati,
P.C.

1. _____

2. _____

3. _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE
SILVERGATE PHARMACEUTICALS, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY)
GREENWOOD VILLAGE, CO

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 23-2415

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☒ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Clark Lin/

Date July 23, 2020

Typed or printed name Clark Y. Lin

Registration No. 67,024



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	10/31/2018	Gerold L. Mosher	43060-707.304	3572
21971 7590 07/31/2020 WILSON, SONSINI, GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 94304-1050			EXAMINER RAO, SAVITHA M	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			07/31/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Response to Rule 312 Communication	Application No. 16/177,159	Applicant(s) Mosher et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☒ The amendment filed on 22 July 2020 under 37 CFR 1.312 has been considered, and has been:

a) ☒ entered.

b) ☒ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

/SAVITHA M RAO/ Primary Examiner, Art Unit 1629	
--	--

Notice of Allowability	Application No. 16/177,159	Applicant(s) Mosher et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 05/15/2020.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 1-11,15,17,19-26,29 and 31-36. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov**.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: ____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. <input type="checkbox"/> Notice of References Cited (PTO-892) 2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>06/05/2020</u> . 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. <input checked="" type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date. <u>07/01/2020</u> .	5. <input type="checkbox"/> Examiner's Amendment/Comment 6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance 7. <input type="checkbox"/> Other _____.
--	--

/SAVITHA M RAO/
Primary Examiner, Art Unit 1629

Application/Control Number: 16/177,159
Art Unit: 1629

Page 2

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-11, 15, 17, 19-26, 29 and 31-36 are pending in the instant application.

Applicants representative Mr. Clark Lin interviewed with the examiner to discuss the claim amendments and the submitted affidavit on 7/1/2020. Please see the attached interview summary for details.

Information Disclosure Statement

The information disclosure statement (IDS) dated 06/05/2020 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Terminal disclaimer

The terminal disclaimer filed on 08/01/2019 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **US patents 9669008, 9808442, 10039745 and 10154987 and US application 16/242898** have been reviewed and is accepted. The terminal disclaimer has been recorded.

Rule 37 CFR 1.132 Declaration

Applicant's submission of the declarations of Gerold Mosher under 37 CFR 1.132 filed 05/15/2020 is acknowledged. The declarations is found to be persuasive in

Application/Control Number: 16/177,159

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Art Unit: 1629

overcoming the outstanding rejections set forth in the non-final rejection dated 01/07/2020.

REASONS FOR ALLOWANCE

In view of the applicants claim amendments, arguments and the declaration filed on 05/15/2020 and the following examiners statement of reasons for allowance, claims 1-11, 15, 17, 19-26, 29 and 31-36 are found to be allowable.

Following a diligent search it was determined that the prior art neither teaches nor provides adequate motivation to arrive at the instantly claimed oral liquid formulation, comprising: (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation; (iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens; and (iv) water; wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a the given storage period of at least 12 months at about 5 ± 30 C.

Conclusion

Claims 1-11, 15, 17, 19-26, 29 and 31-36 (renumbered 1-28) are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Application/Control Number: 16/177,159

Page 4

Art Unit: 1629

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA M RAO/

Primary Examiner, Art Unit 1629



UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/177,159	09/29/2020	10786482	43060-707.304	3572

21971 7590 09/09/2020

WILSON, SONSINI, GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Gerold L. Mosher, Kansas City, MO;
 Silvergate Pharmaceuticals, Inc., Greenwood Village, CO;
 David W. Miles, Kansas City, MO;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

PTO/AIA/15 (10-17)

Approved for use through 11/30/2020. OMB 0651-0032

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL <i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i>		Attorney Docket No. 43060-707.307	
		First Named Inventor Gerold L. MOSHER	
		Title ENALAPRIL FORMULATIONS	
		Priority Mail Express® Label No. Filed Electronically via EFS-Web on January 8, 2019	

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
1. <input type="checkbox"/> Fee Transmittal Form (PTO/SB/17 or equivalent) 2. <input type="checkbox"/> Applicant asserts small entity status. See 37 CFR 1.27 3. <input type="checkbox"/> Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. <input checked="" type="checkbox"/> Specification [Total Pages <u>51</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. <input checked="" type="checkbox"/> Drawing(s) (35 U.S.C. 113) [Total Sheets <u>2</u>] 6. Inventor's Oath or Declaration [Total Pages <u>2</u>] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. <input type="checkbox"/> Newly executed (original or copy) b. <input checked="" type="checkbox"/> A copy from a prior application (37 CFR 1.63(d)) 7. <input checked="" type="checkbox"/> Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) <input type="checkbox"/> Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. <input type="checkbox"/> Computer Readable Form (CRF) b. <input type="checkbox"/> Specification Sequence Listing on: i. <input type="checkbox"/> CD-ROM or CD-R (2 copies); or ii. <input type="checkbox"/> Paper c. <input type="checkbox"/> Statements verifying identity of above copies	ACCOMPANYING APPLICATION PAPERS 10. <input type="checkbox"/> Assignment Papers (cover sheet & document(s)) Name of Assignee _____ 11. <input checked="" type="checkbox"/> 37 CFR 3.73(c) Statement <input checked="" type="checkbox"/> Power of Attorney (when there is an assignee) 12. <input type="checkbox"/> English Translation Document (if applicable) 13. <input type="checkbox"/> Information Disclosure Statement (PTO/SB/08 or PTO-1449) <input type="checkbox"/> Copies of citations attached 14. <input type="checkbox"/> Preliminary Amendment 15. <input type="checkbox"/> Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. <input type="checkbox"/> Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. <input type="checkbox"/> Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 18. <input checked="" type="checkbox"/> Other: Certification and Request for Prioritized Examination Under 37 CFR 1.102(e) - 1 pp. _____ _____ _____

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
 (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS					
<input checked="" type="checkbox"/> The address associated with Customer Number: <u>21971</u> OR <input type="checkbox"/> Correspondence address below					
Name _____					
Address _____					
City _____		State _____		Zip Code _____	
Country _____		Telephone _____		Email _____	

Signature	/Clark Lin/	Date	August 12, 2020
Name (Print/Type)	Clark Y. Lin	Registration No. (Attorney/Agent)	67024

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.307
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.</p> <p>This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor	1				<input type="button" value="Remove"/>	
Legal Name						
Prefix	Given Name	Middle Name	Family Name	Suffix		
	Gerold	L.	MOSHER			
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service						
City	Kansas City	State/Province	MO	Country of Residence	US	
Mailing Address of Inventor:						
Address 1	12215 Avila Drive					
Address 2						
City	Kansas City	State/Province	MO			
Postal Code	64145	Country	US			
Inventor	2				<input type="button" value="Remove"/>	
Legal Name						
Prefix	Given Name	Middle Name	Family Name	Suffix		
	David	W.	MILES			
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service						
City	Kansas City	State/Province	MO	Country of Residence	US	
Mailing Address of Inventor:						
Address 1	12309 Wyandotte Street					
Address 2						
City	Kansas City	State/Province	MO			
Postal Code	64145	Country	US			
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. <input type="button" value="Add"/>						

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.307
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

☐ An Address is being provided for the correspondence information of this application.

Customer Number	21971		
Email Address	patentdocket@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	ENALAPRIL FORMULATIONS		
Attorney Docket Number	43060-707.307	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	2	Suggested Figure for Publication (if any)	1

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:
☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	<input type="radio"/> US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	21971		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.307
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
	Continuation of	16/883553	2020-05-26		
Prior Application Status	Pending	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
16/883553	Continuation of	16/242898	2019-01-08		
Prior Application Status	Pending	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
16/242898	Continuation of	16/177159	2018-10-31		
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/177159	Continuation of	16/003994	2018-06-08	10154987	2018-12-18
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/003994	Continuation of	15/802341	2017-11-02	10039745	2018-08-07
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/802341	Continuation of	15/613622	2017-06-05	9808442	2017-11-07
Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/613622	Continuation of	15/081603	2016-03-25	9669008	2017-06-06
Prior Application Status	Expired	Remove			
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
15/081603	Claims benefit of provisional	62/310198	2016-03-18		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.					Add

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.307
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)	Remove

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.307
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.307
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant	1	<input type="button" value="Remove"/>
<p>If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.</p> <p style="text-align: right;"><input type="button" value="Clear"/></p>		
<input checked="" type="radio"/> Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
<div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
Name of the Deceased or Legally Incapacitated Inventor: <div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>		
Organization Name	Silvergate Pharmaceuticals, Inc.	
Mailing Address Information For Applicant:		
Address 1	6251 Greenwood Plaza Blvd., Bldg. 6, Suite 101	
Address 2		
City	Greenwood Village	State/Province
Country	US	Postal Code
Phone Number		Fax Number
Email Address		
Additional Applicant Data may be generated within this form by selecting the Add button. <input type="button" value="Add"/>		

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.307
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

Assignee	1			
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.				
				<input type="button" value="Remove"/>
If the Assignee or Non-Applicant Assignee is an Organization check here.				<input type="checkbox"/>
Prefix	Given Name	Middle Name	Family Name	Suffix
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Mailing Address Information For Assignee including Non-Applicant Assignee:				
Address 1		<input type="text"/>		
Address 2		<input type="text"/>		
City	<input type="text"/>	State/Province	<input type="text"/>	
Country i	<input type="text"/>	Postal Code	<input type="text"/>	
Phone Number	<input type="text"/>	Fax Number	<input type="text"/>	
Email Address	<input type="text"/>			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.				<input type="button" value="Add"/>

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is **not** checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Clark Lin/		Date (YYYY-MM-DD)	2020-08-12
First Name	Clark	Last Name	Lin	Registration Number 67024
Additional Signature may be generated within this form by selecting the Add button.				<input type="button" value="Add"/>

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	43060-707.307
		Application Number	
Title of Invention	ENALAPRIL FORMULATIONS		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ENALAPRIL FORMULATIONS

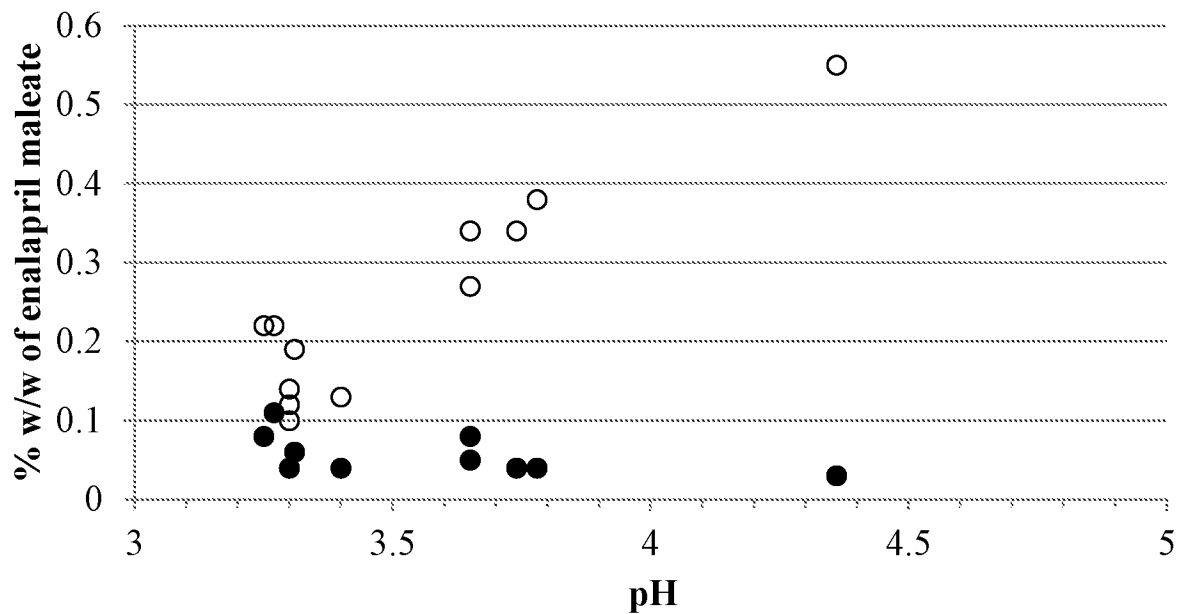
ABSTRACT OF THE DISCLOSURE

Provided herein are stable enalapril oral liquid formulations. Also provided herein are methods of using enalapril oral liquid formulations for the treatment of certain diseases including hypertension, heart failure and asymptomatic left ventricular dysfunction.

1/2

FIG. 1

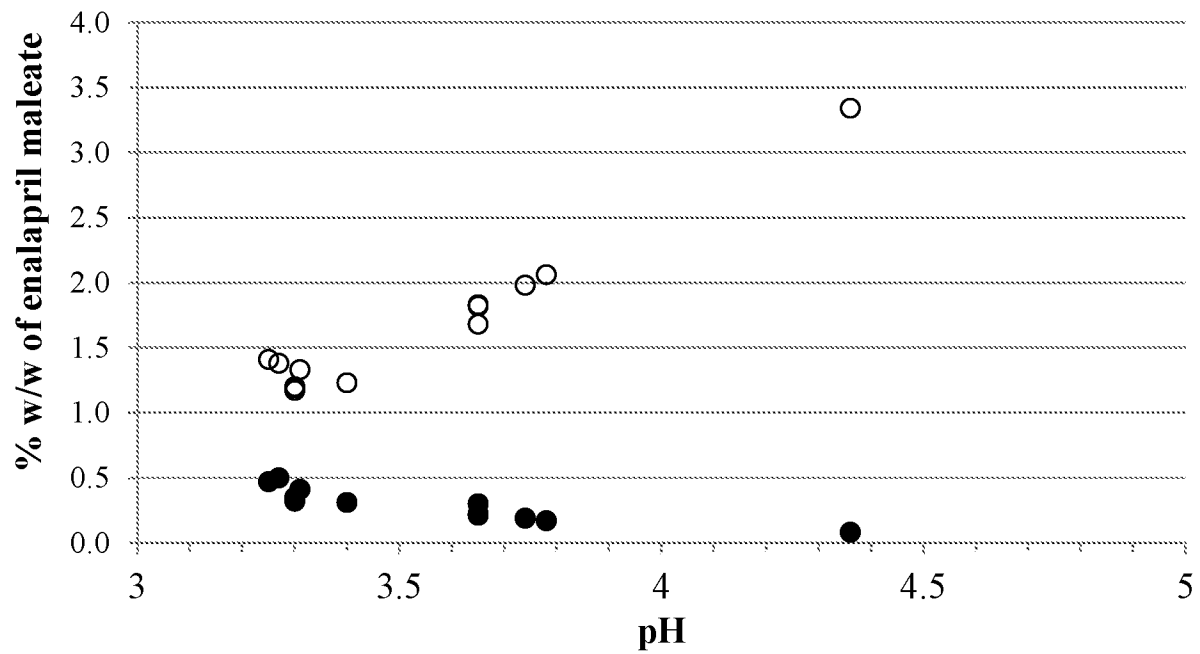
● Enalapril diketopiperazine; ○ Enalaprilat



2/2

FIG. 2

● Enalapril diketopiperazine; ○ Enalaprilat



Doc Code: TRACK1.REQ

Document Description: TrackOne Request

PTO/AIA/424 (04-14)

**CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION
UNDER 37 CFR 1.102(e) (Page 1 of 1)**

First Named Inventor:	Gerold L. MOSHER	Nonprovisional Application Number (if known):	
Title of Invention:	ENALAPRIL FORMULATIONS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. ☒ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

- i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.
---OR---
- (b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.
- ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, or the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

- i. A request for continued examination has been filed with, or prior to, this form.
- ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
- iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
- iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
- v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Clark Lin/	Date August 12, 2020
Name (Print/Typed) Clark Y. Lin	Practitioner Registration Number 67024
<p>Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.*</p>	
<p><input checked="" type="checkbox"/> *Total of <u>1</u> forms are submitted.</p>	

Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)Applicant/Patent Owner: Silvergate Pharmaceuticals, Inc.Application No./Patent No.: 15/081,603Filed/Issue Date: March 25, 2016Titled: ENALAPRIL FORMULATIONSSilvergate Pharmaceuticals, Inc., a Corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.
2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):
- ☐ The extent (by percentage) of its ownership interest is ____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.
- ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

- A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 038792, Frame 0116, or for which a copy thereof is attached.

- B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[Page 1 of 2]

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.☐ Additional documents in the chain of title are listed on a supplemental sheet(s).☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Clark Lin/

June 8, 2016

Signature

Date

Clark Y. Lin

67,024

Printed or Typed Name

Title or Registration Number

[Page 2 of 2]

WSGR Docket No. 43060-707.307

PATENT APPLICATION
ENALAPRIL FORMULATIONS

Inventors: Gerold L. Mosher,
Citizen of the United States of America, Residing at
12215 Avila Drive
Kansas City, MO 64145

David W. Miles,
Citizen of the United States of America, Residing at
12309 Wyandotte Street
Kansas City, MO 64145

Assignees: Silvergate Pharmaceuticals, Inc.
6251 Greenwood Plaza Blvd., Bldg. 6, Suite 101
Greenwood Village, CO 80111

a Delaware Corporation

Entity: Large business concern



Wilson Sonsini Goodrich & Rosati
PROFESSIONAL CORPORATION

650 Page Mill Road
Palo Alto, CA 94304
(650) 493-9300 (Main)
(650) 493-6811 (Facsimile)

Filed Electronically on: August 12, 2020

ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

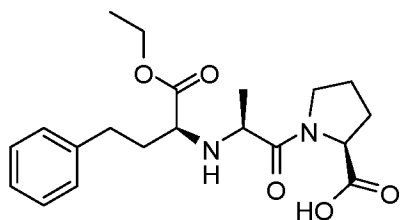
[0001] This application is a continuation of U.S. Patent Application No. 16/883,553, filed May 26, 2020 which is a continuation of U.S. Patent Application No. 16/242,898, filed January 8, 2019, which is a continuation of 16/177,159, filed October 31, 2018, which is a continuation of U.S. Patent Application No. 16/003,994, filed June 8, 2018 (now U.S. Patent No. 10,154,987, issued December 18, 2018), which is a continuation of U.S. Patent Application No. 15/802,341, filed November 2, 2017 (now U.S. Patent No. 10,039,745, issued August 7, 2018), which is a continuation of U.S. Patent Application No. 15/613,622, filed June 5, 2017 (now U.S. Patent No. 9,808,442, issued November 7, 2017), which is a continuation of U.S. Patent Application No. 15/081,603, filed March 25, 2016 (now U.S. Patent No. 9,669,008, issued June 06, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed March 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

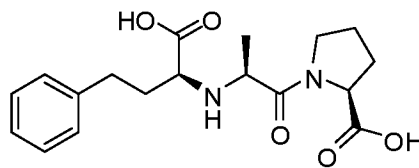
[0002] Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

[0003] A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptidyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

[0004] Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



Enalapril



Enalaprilat

[0005] Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

[0006] Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3 °C for at least 12 months.

[0007] In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25 % (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18 % (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47 % (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11 % (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25 % (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3 °C for at least 18 months. In some embodiments, the formulation is stable at about 5±3 °C for at least 24

months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0008] In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0009] In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 18 months. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0010] In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3 % (w/w of solids) enalapril maleate; (ii) about 13.5 % (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2 % (w/w of solids) citric acid; (iv) about 19.3 % (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0011] In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9 % (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 18 months. In some embodiments, the formulation is stable at about 5 ± 3 °C for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0012] In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the

formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months.

[0013] Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0014] In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

[0015] Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0016] In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

[0017] Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments,

the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

[0018] Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5 ± 3 °C for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

[0019] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0021] FIG. 1: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5°C.

[0022] FIG. 2: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22°C).

DETAILED DESCRIPTION OF THE INVENTION

[0023] Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

[0024] It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rendering the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

[0025] Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

[0026] For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

[0027] Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

[0028] The present embodiments described herein provide a safe and effective oral administration of enalapril for the treatment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

[0029] As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in

the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

[0030] Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

[0031] Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

[0032] In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

[0033] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84

mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02 mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

[0034] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 % w/w to about 30 % w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 % w/w, about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 % w/w, about 14 % w/w, about 14.5 % w/w, about 15 % w/w, about 15.1 % w/w, about 15.2 % w/w, about 15.3 % w/w, about 15.4 % w/w, about 15.5 % w/w, about 15.6 % w/w, about 15.7 % w/w, about 15.8 % w/w, about 15.9 % w/w, about 16 % w/w, about 16.1 % w/w, about 16.2 % w/w, about 16.3 % w/w, about 16.4 % w/w, about 16.5 % w/w, about 16.6 % w/w, about 16.7 % w/w, about 16.8 % w/w, about 16.9 % w/w, about 17 % w/w, about 17.1 % w/w, about 17.2 % w/w, about 17.3 % w/w, about 17.4 % w/w, about 17.5 % w/w, about 17.6 % w/w, about 17.7 % w/w, about 17.8 % w/w, about 17.9 % w/w, about 18 % w/w, about 18.1 % w/w, about 18.2 % w/w, about 18.3 % w/w, about 18.4 % w/w, about 18.5 % w/w, about 18.6 % w/w, about 18.7 % w/w, about 18.8 % w/w, about 18.9 % w/w, about 19 % w/w, about 19.1 % w/w, about 19.2 % w/w, about 19.3 % w/w, about 19.4 % w/w, about 19.5 % w/w, about 19.6 % w/w, about 19.7 % w/w, about 19.8 % w/w, about 19.9 % w/w, about 20 % w/w, about 20.1 % w/w, about 20.2 % w/w, about 20.3 % w/w, about 20.4 % w/w, about 20.5 % w/w, about 20.6 % w/w, about 20.7 % w/w, about 20.8 % w/w, about 20.9 % w/w, about 21 % w/w, about 21.1 % w/w, about 21.2 % w/w, about 21.3 % w/w, about 21.4 % w/w, about 21.5 % w/w, about 21.6 % w/w, about 21.7 % w/w, about 21.8 % w/w, about 21.9 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5

% w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10 % w/w to about 25 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5 % w/w of the solids in the oral liquid formulation.

[0035] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1 % w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1 % w/w, about 0.15 % w/w, about 0.2 % w/w, about 0.25 % w/w, about 0.3 % w/w, about 0.35 % w/w, about 0.4 % w/w, about 0.45 % w/w, about 0.5 % w/w, about 0.55 % w/w, about 0.6 % w/w, about 0.65 % w/w, about 0.7 % w/w, about 0.75 % w/w, about 0.8 % w/w, about 0.85 % w/w, about 0.9 % w/w, about 0.95 % w/w, or about 1 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4 % w/w to about 0.7 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5 % w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6 % w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

[0036] Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

[0037] Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate,

saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005--maltodextrin, sorbitol, and fructose combination and Product Code 918.010--water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Virginia Dare), Maltisweet™ (maltitol solution, Ingredion), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

[0038] In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

[0039] In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

[0040] In some embodiments, sucralose is present in about 1 % w/w to about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about

13.5 % w/w, about 14% w/w, about 14.5 % w/w, about 15 % w/w, about 15.5 % w/w, about 16 % w/w, about 16.5 % w/w, about 17 % w/w, about 17.5 % w/w, about 18 % w/w, about 18.5 % w/w, about 19 % w/w, about 19.5 % w/w, about 20 % w/w, about 20.5 % w/w, about 21 % w/w, about 21.5 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5 % w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8 % w/w to about 18 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5 % w/w of the solids in the oral liquid formulation.

[0041] In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

[0042] In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

[0043] In some embodiments, xylitol is present in about 80 % w/w to about 99 % w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80 % w/w, about 81 % w/w, about 82 % w/w, about 83 % w/w, about 84 % w/w, about 85 % w/w, about 86 % w/w, about 87 % w/w, about 88 % w/w, about 89 % w/w, about 90 % w/w, about 91 % w/w, about 92 % w/w, about 93 % w/w, about 94 % w/w, about 95 % w/w, about 96 % w/w, about 97 % w/w, about 98 % w/w, or about 99 % w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96 % w/w to about 98 % w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96 % w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

[0044] Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

[0045] In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

[0046] In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

[0047] In some embodiments, the preservative is sodium benzoate.

[0048] In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

[0049] In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

[0050] In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about

1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

[0051] In some embodiments, sodium benzoate is present in about 1% w/w to about 30 % w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 % w/w, about 14 % w/w, about 14.5 % w/w, about 15 % w/w, about 15.1 % w/w, about 15.2 % w/w, about 15.3 % w/w, about 15.4 % w/w, about 15.5 % w/w, about 15.6 % w/w, about 15.7 % w/w, about 15.8 % w/w, about 15.9 % w/w, about 16 % w/w, about 16.1 % w/w, about 16.2 % w/w, about 16.3 % w/w, about 16.4 % w/w, about 16.5 % w/w, about 16.6 % w/w, about 16.7 % w/w, about 16.8 % w/w, about 16.9 % w/w, about 17 % w/w, about 17.1 % w/w, about 17.2 % w/w, about 17.3 % w/w, about 17.4 % w/w, about 17.5 % w/w, about 17.6 % w/w, about 17.7 % w/w, about 17.8 % w/w, about 17.9 % w/w, about 18 % w/w, about 18.1 % w/w, about 18.2 % w/w, about 18.3 % w/w, about 18.4 % w/w, about 18.5 % w/w, about 18.6 % w/w, about 18.7 % w/w, about 18.8 % w/w, about 18.9 % w/w, about 19 % w/w, about 19.1 % w/w, about 19.2 % w/w, about 19.3 % w/w, about 19.4 % w/w, about 19.5 % w/w, about 19.6 % w/w, about 19.7 % w/w, about 19.8 % w/w, about 19.9 % w/w, about 20 % w/w, about 20.1 % w/w, about 20.2 % w/w, about 20.3 % w/w, about 20.4 % w/w, about 20.5 % w/w, about 20.6 % w/w, about 20.7 % w/w, about 20.8 % w/w, about 20.9 % w/w, about 21 % w/w, about 21.1 % w/w, about 21.2 % w/w, about 21.3 % w/w, about 21.4 % w/w, about 21.5 % w/w, about 21.6 % w/w, about 21.7 % w/w, about 21.8 % w/w, about 21.9 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5 % w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5 % w/w of the solids in the oral liquid formulation.

[0052] In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1 % w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1 % w/w, about 0.15 % w/w, about 0.2 % w/w, about 0.25 % w/w, about 0.3 % w/w, about 0.35 % w/w, about 0.4 % w/w, about 0.45 % w/w, about 0.5 % w/w, about 0.55 % w/w, about 0.6 % w/w, about 0.65 % w/w, about 0.7 % w/w, about 0.75 % w/w, about 0.8 % w/w, about 0.85 % w/w, about 0.9 % w/w, about 0.95 % w/w, or about 1 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4 % w/w to about 0.7 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6 % w/w of the solids in the oral liquid formulation.

[0053] In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

[0054] In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

[0055] In some embodiments, the paraben or mixture of parabens is present in about 2 % w/w to about 30 % w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2 % w/w, about 3 % w/w, about 4 % w/w, about 5 % w/w, about 6 % w/w, about 7 % w/w, about 8 % w/w, about 9 % w/w, about 10 % w/w, about 11 % w/w, about 12 % w/w, about 13 % w/w, about 14 % w/w, about 15 % w/w, about 16 % w/w, about 17 % w/w, about 18 % w/w, about 19 % w/w, about 20 % w/w, about 21 % w/w, about 22 % w/w, about 23 % w/w, about 24 % w/w, about 25 % w/w, about 26 % w/w, about 27 % w/w, about 28 % w/w, about 29 % w/w, or about 30 % w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2 % w/w to about 3 % w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23 % w/w to about 26 % w/w of the

solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26 % w/w to about 30 % w/w of the solids in the oral liquid formulation.

Sweetener and preservative incompatibility

[0056] Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

[0057] In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

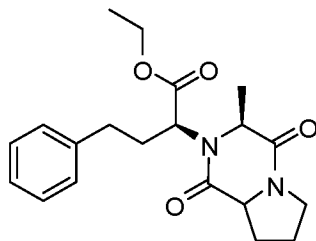
[0058] Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

[0059] In some embodiments, the oral liquid formulation comprises a buffer.

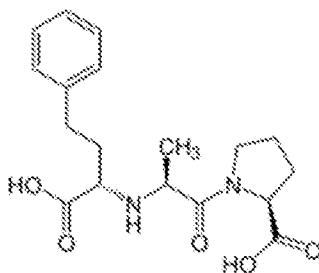
[0060] In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

[0061] In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

[0062] In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



enalapril diketopiperazine;



enalaprilat

[0063] In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. 1 and FIG. 2). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

[0064] In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

[0065] In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

[0066] In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM,

about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

[0067] In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

[0068] In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1

mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

[0069] In some embodiments, citric acid is present in about 10 % w/w to about 50 % w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10 % w/w, about 11 % w/w, about 12 % w/w, about 13 % w/w, about 14 % w/w, about 15 % w/w, about 16 % w/w, about 17 % w/w, about 18 % w/w, about 19 % w/w, about 20 % w/w, about 21 % w/w, about 22 % w/w, about 23 % w/w, about 24 % w/w, about 25 % w/w, about 26 % w/w, about 27 % w/w, about 28 % w/w, about 29 % w/w, about 30 % w/w, about 31 % w/w, about 32 % w/w, about 33 % w/w, about 34 % w/w, about 35 % w/w, about 36 % w/w, about 37 % w/w, about 38 % w/w, about 39 % w/w, about 40 % w/w, about 41 % w/w, about 42 % w/w, about 43 % w/w, about 44 % w/w, about 45 % w/w, about 46 % w/w, about 47 % w/w, about 48 % w/w, about 49 % w/w, about 50 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19 % w/w of the solids in the oral liquid formulation.

[0070] In some embodiments, citric acid is present in about 1 % w/w to about 5 % w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1 % w/w, about 1.1 % w/w, about 1.2 % w/w, about 1.3 % w/w, about 1.4 % w/w, about 1.5 % w/w, about 1.6 % w/w, about 1.7 % w/w, about 1.8 % w/w, about 1.9 % w/w, about 2 % w/w, about 2.1 % w/w, about 2.2 % w/w, about 2.3 % w/w, about 2.4 % w/w, about 2.5 % w/w, about 2.6 % w/w, about 2.7 % w/w, about 2.8 % w/w, about 2.9 % w/w, about 3 % w/w, about 3.1 % w/w, about 3.2 % w/w, about 3.3 % w/w, about 3.4 % w/w, about 3.5 % w/w, about 3.6 % w/w, about 3.7 % w/w, about 3.8 % w/w, about 3.9 % w/w, about 4 % w/w, about 4.1 % w/w, about 4.2 % w/w, about 4.3 % w/w, about 4.4 % w/w, about 4.5 % w/w, about 4.6 % w/w, about 4.7 % w/w, about 4.8 % w/w, about 4.9 % w/w, or about 5 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1 % w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6 % w/w of the solids in the oral liquid formulation.

[0071] In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid

formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/ml, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

[0072] In some embodiments, sodium citrate dihydrate is present in about 1 % w/w to about 15 % w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1 % w/w, about 1.1 % w/w, about 1.2 % w/w, about 1.3 % w/w, about 1.4 % w/w, about 1.5 % w/w, about 1.6 % w/w, about 1.7 % w/w, about 1.8 % w/w, about 1.9 % w/w, about 2 % w/w, about 2.1 % w/w, about 2.2 % w/w, about 2.3 % w/w, about 2.4 % w/w, about 2.5 % w/w, about 2.6 % w/w, about 2.7 % w/w, about 2.8 % w/w, about 2.9 % w/w, about 3 % w/w, about 3.1 % w/w, about 3.2 % w/w, about 3.3 % w/w, about 3.4 % w/w, about 3.5 % w/w, about 3.6 % w/w, about 3.7 % w/w, about 3.8 % w/w, about 3.9 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 % w/w, about 14 % w/w, about 14.5 % w/w, about 15 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5 % w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5 % w/w of the solids

in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9 % w/w of the solids in the oral liquid formulation.

[0073] In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional excipients

[0074] In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

[0075] Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

[0076] In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

[0077] In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

[0078] Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches,

pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

[0079] Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, PA: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, PA: Mack Publishing Co 1975); Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, NY: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

[0080] The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

[0081] The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95 % or greater of the initial enalapril amount and about 5 % w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5 % w/w, about 4 % w/w, about 3 % w/w, about 2.5 % w/w, about 2 % w/w, about 1.5 % w/w, about 1 % w/w, or about 0.5 % w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1 % w/w total impurities or related substances.

[0082] At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5 ± 3 °C. In some embodiments, refrigerated condition is about 2 °C, about 2.1 °C, about 2.2 °C, about 2.3 °C, about 2.4 °C, about 2.5 °C, about 2.6 °C, about 2.7 °C, about 2.8 °C, about 2.9 °C, about 3 °C, about 3.1 °C, about 3.2 °C, about 3.3 °C, about 3.4 °C, about 3.5 °C, about 3.6 °C, about 3.7 °C, about 3.8 °C, about 3.9 °C, about 4 °C, about 4.1 °C, about 4.2 °C,

about 4.3 °C, about 4.4 °C, about 4.5 °C, about 4.6 °C, about 4.7 °C, about 4.8 °C, about 4.9 °C, about 5 °C, about 5.1 °C, about 5.2 °C, about 5.3 °C, about 5.4 °C, about 5.5 °C, about 5.6 °C, about 5.7 °C, about 5.8 °C, about 5.9 °C, about 6 °C, about 6.1 °C, about 6.2 °C, about 6.3 °C, about 6.4 °C, about 6.5 °C, about 6.6 °C, about 6.7 °C, about 6.8 °C, about 6.9 °C, about 7 °C, about 7.1 °C, about 7.2 °C, about 7.3 °C, about 7.4 °C, about 7.5 °C, about 7.6 °C, about 7.7 °C, about 7.8 °C, about 7.9 °C, or about 8 °C. At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. 25±5 °C; 55±10% RH). In some instances, an accelerated condition is at about 25 °C, about 30 °C, about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C or about 60 °C. In other instances, an accelerated condition is above 55% RH, about 65 % RH, about 70 % RH, about 75 % RH or about 80 % RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40 °C at 75±5 % RH humidity.

Enalapril Oral Powder Formulation

[0083] In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

[0084] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30 % w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5 % w/w, about 1 % w/w, about 1.5 % w/w, about 2 % w/w, about 2.5 % w/w, about 3 % w/w, about 3.5 % w/w, about 4 % w/w, about 4.5 % w/w, about 5 % w/w, about 5.5 % w/w, about 6 % w/w, about 6.5 % w/w, about 7 % w/w, about 7.5 % w/w, about 8 % w/w, about 8.5 % w/w, about 9 % w/w, about 9.5 % w/w, about 10 % w/w, about 10.5 % w/w, about 11 % w/w, about 11.5 % w/w, about 12 % w/w, about 12.5 % w/w, about 13 % w/w, about 13.5 %

w/w, about 14% w/w, about 14.5 % w/w, about 15 % w/w, about 15.5 % w/w, about 16 % w/w, about 16.5 % w/w, about 17 % w/w, about 17.5 % w/w, about 18 % w/w, about 18.5 % w/w, about 19 % w/w, about 19.5 % w/w, about 20 % w/w, about 20.5 % w/w, about 21 % w/w, about 21.5 % w/w, about 22 % w/w, about 22.5 % w/w, about 23 % w/w, about 23.5 % w/w, about 24 % w/w, about 24.5 % w/w, about 25 % w/w, about 25.5 % w/w, about 26 % w/w, about 26.5 % w/w, about 27 % w/w, about 27.5 % w/w, about 28 % w/w, about 28.5 % w/w, about 29 % w/w, about 29.5 % w/w, or about 30 % w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5 % w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5 % w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5 % w/w of the powder formulation. In some embodiments, enalapril is present in about 18 % w/w of the powder formulation.

[0085] In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1 % w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1 % w/w, about 0.15 % w/w, about 0.2 % w/w, about 0.25 % w/w, about 0.3 % w/w, about 0.35 % w/w, about 0.4 % w/w, about 0.45 % w/w, about 0.5 % w/w, about 0.55 % w/w, about 0.6 % w/w, about 0.65 % w/w, about 0.7 % w/w, about 0.75 % w/w, about 0.8 % w/w, about 0.85 % w/w, about 0.9 % w/w, about 0.95 % w/w, or about 1 % w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4 % w/w to about 0.7 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45 % w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6 % w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4 % w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5 % w/w of the powder formulation.

[0086] Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1 % w/w to about 30 % w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1 % w/w to about 30 % w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1 % w/w to about 30 % w/w of the solids in the oral liquid formulation, in an analogous enalapril

powder formulation sodium benzoate is present in about 1 % w/w to about 30 % w/w in the powder formulation.

[0087] Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

[0088] Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

[0089] In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

[0090] Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon

dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

[0091] In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

[0092] In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

[0093] In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

[0094] Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, PA: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, PA: Mack Publishing Co 1975); Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, NY: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

[0095] In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

[0096] Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof; and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2x10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

[0097] The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder

formulations having about 95 % or greater of the initial enalapril amount and 5 % w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5 % w/w, about 4 % w/w, about 3 % w/w, about 2.5 % w/w, about 2 % w/w, about 1.5 % w/w, about 1 % w/w, or about 0.5 % w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2 % w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1 % w/w total impurities or related substances.

[0098] At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25 ± 4 °C; 55 ± 10 % RH). In some instances, an accelerated condition is at about 30 °C, about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C or about 60 °C. In other instances, an accelerated condition is above 65 % RH, about 70 % RH, about 75 % RH or about 80 % RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40 °C at 75 ± 5 % RH humidity.

Kits and Articles of Manufacture

[0099] For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

[00100] A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

[00101] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

[00102] Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

[00103] In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

[00104] In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described

herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

[00105] In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

[00106] In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

[00107] Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

[00108] In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but

can nevertheless be determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

[00109] In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76, mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

[00110] In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg,

about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

[00111] In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

[00112] In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max} , T_{max} , C_{min} , $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

[00113] Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[00114] In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular

disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

[00115] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

[00116] In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00117] In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, *i.e.*, administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (*e.g.* drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

[00118] In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

[00119] In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10

minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

[00120] In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

[00121] The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

[00122] Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propranolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxymethamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., diltiazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, losartan, eprosartan, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

[00123] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[00124] As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

[00125] The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.” The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[00126] “Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

[00127] As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

[00128] “Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term “administering”, when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. “Administering” a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

[00129] The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms “patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic

species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

[00130] By “pharmaceutically acceptable”, it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[00131] The term “pharmaceutical composition” shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[00132] A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a “therapeutically effective amount” or “effective amount” of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

[00133] The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the

condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, “treat,” “treated,” “treatment,” or “treating” includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60 °C.

[00134] Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60 °C heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration						
Component	Formulation (mM citrate)					
	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

[00135] The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)						
Hours at 60 °C	Formulation					
	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60 °C.

[00136] Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60 °C heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations			
Component	Formulation		
	B1 (5mM citrate)	B2 (10mM citrate)	B3 (20mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7

Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

[00137] The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)			
Hours at 60°C	Formulation		
	B1 (5mM citrate)	B2 (10mM citrate)	B3 (20mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives.

[00138] Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5 °C ± 3°C, at room temperature (19-23 °C) and at 40°C ± 2 °C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations					
Powder Formulation (grams)					
Component	C1	C2	C3	C4	C5
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

[00139] The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	°C	Weeks	C1	C2	C3	C4	C5
Liquid Formulations							
Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
		4	0.02	0.03	0.03	0.03	0.02
		8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.04	0.02	0.02
		4	0.05	0.09	0.11	0.05	0.04
		8	0.08	0.17	0.19		
	40	0	0.03	0.04	0.04	0.02	0.02
		4	0.35	0.91	1.10	0.31	0.21
		8	0.65	1.80	2.05		
	5	0	0.18	0.14	0.12	0.13	0.19
		4	0.18	0.15	0.12	0.43	0.53
		8	0.55	0.38	0.34		
Enalaprilat	19-23	0	0.18	0.14	0.12	0.13	0.19
		4	1.35	0.83	0.80	1.75	2.29
		8	3.34	2.06	1.98		
	40	0	0.18	0.14	0.12	0.13	0.19
		4	10.49	6.08	6.11	12.30	16.14
		8	24.37	14.12	14.22		

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative.

[00140] Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The

amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, at room temperature ($19\text{-}23^{\circ}\text{C}$) and at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations						
Powder Formulation (grams)						
Component	D1	D2	D3	D4	D5	D6
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

[00141] The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)								
Storage			Formulation					
	°C	Weeks	D1	D2	D3	D4	D5	D6
Liquid Formulations								
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		
	40	0	0.03	0.02	0.03	0.03	0.13	0.14

4	4.76	4.42	4.76	6.45	5.55	5.24
8	8.95	8.64	9.61	12.94	12.73	12.18
12	11.01	10.64	11.41	16.16		
26	17.18	17.11	18.30	27.36		

Example E: Stability of Solution Formulations of Enalapril Maleate.

[00142] Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5 °C ± 3 °C, at room temperature (19-23 °C) and at 40 °C ± 2 °C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)						
Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

[00143] The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage			Formulation				
	°C	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04

		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
19-23	0	0.01	0.01	0.01	0.01	0.01	0.01	0.01
	4	0.22	0.23	0.21	0.20	0.16	0.15	
	8	0.35	0.35	0.32	0.31	0.29	0.28	
	12	0.58	0.59	0.53	0.51	0.48	0.45	
	26	1.10	1.10	1.00	0.95	0.97	0.92	
	52					2.30	2.15	
	62	3.02	3.04	2.75	2.64			
40	0	0.01	0.01	0.01	0.01	0.01	0.01	0.01
	4	2.65	2.71	2.60	2.42	1.76	1.68	
	8	4.02	3.99	3.99	3.62	3.37	3.13	
	12	6.72	6.42	6.47	6.00	5.53	5.29	
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		
	19-23	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.65	0.65	0.68	0.70	0.50	0.46
		8	1.17	1.19	1.20	1.23	1.03	0.95
		12	1.67	1.69	1.72	1.80	1.30	1.21
		26	3.36	3.38	3.42	3.57	3.07	2.90
		52					6.32	5.88
		62	7.99	8.02	8.04	8.57		
	40	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	4.85	4.93	5.19	5.42	3.33	3.25
		8	8.08	8.06	8.56	9.01	6.65	6.35
		12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5 °C and 19-23 °C.

[00144] The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in Figure 1 (5°C ± 3 °C) and Figure 2 (19-23 °C storage). These formulations all contained 20mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

[00145] Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10mg Enalapril Maleate Oral Solution vs. 10mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

[00146] The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

[00147] Study design: Thirty-two healthy adult subjects received a single 10mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

[00148] During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

[00149] Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

[00150] Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned

Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_{\max} were approximately 115% and 109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on $\ln(C_{\max})$, was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on $\ln(AUC_{\text{last}})$ and $\ln(AUC_{\text{inf}})$, was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

[00151] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
 - (iii) a preservative, wherein the preservative is a paraben or a mixture of parabens; and
 - (iv) water;
 wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
 wherein the formulation is stable at about 5 ± 3 °C for at least 12 months; and
 wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
2. The stable oral liquid formulation of claim 1, comprising a sweetener.
3. The stable oral liquid formulation of claim 1, comprising a flavoring agent.
4. The stable oral liquid formulation of claim 1, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.
5. The stable oral liquid formulation of claim 1, wherein the buffer concentration is about 10 mM to about 20 mM.
6. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH between about 3 and about 4.
7. The stable oral liquid formulation of claim 1, wherein the buffer maintains the pH at about 3.3.
8. The stable oral liquid formulation of claim 1, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.
9. The stable oral liquid formulation of claim 1, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.
10. The stable oral liquid formulation of claim 1, wherein the preservative is a mixture of parabens.
11. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is methylparaben, ethylparaben, propylparaben, butylparaben, salts thereof, or a combination thereof.
12. The stable oral liquid formulation of claim 1, wherein the preservative is a mixture of methylparaben and propylparaben.

13. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.
14. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation.
15. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.
16. The stable oral liquid formulation of claim 1, wherein the paraben or the mixture of parabens is present at about 2% w/w to about 30% w/w of the solids in the oral liquid formulation.
17. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 18 months.
18. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 24 months.
19. A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
 - (iii) a preservative, wherein the preservative is methylparaben, ethylparaben, propylparaben, butylparaben, or a combination thereof; and
 - (iv) water;wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
wherein the formulation is stable at about $5 \pm 3^{\circ}\text{C}$ for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
20. The stable oral liquid formulation of claim 19, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.
21. The stable oral liquid formulation of claim 19, wherein the buffer concentration is about 10 mM to about 20 mM.
22. The stable oral liquid formulation of claim 19, wherein the buffer maintains the pH between about 3 and about 4.
23. The stable oral liquid formulation of claim 19, wherein the buffer maintains the pH at about 3.3.

24. The stable oral liquid formulation of claim 19, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.
25. The stable oral liquid formulation of claim 19, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.
26. The stable oral liquid formulation of claim 19, wherein the preservative is a mixture of parabens that are selected from methylparaben, ethylparaben, propylparaben, and butylparaben.
27. The stable oral liquid formulation of claim 19, wherein the preservative is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.
28. The stable oral liquid formulation of claim 19, wherein the preservative is present at about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation.
29. The stable oral liquid formulation of claim 19, wherein the preservative is present at about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.
30. A stable oral liquid formulation, consisting essentially of:
 - (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
 - (ii) a buffer to maintain the pH about 4.5 or below;
 - (iii) a preservative, wherein the preservative is methylparaben, ethylparaben, propylparaben, butylparaben, or a combination thereof; and
 - (iv) water;wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
wherein the formulation is stable at about 5 ± 3 °C for at least 12 months; and
wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/991,575	08/12/2020		2720	43060-707.307	30	3

CONFIRMATION NO. 7887

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WILSON, SONSINI, GOODRICH & ROSATI
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0000000119311463

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Inventor(s)

Gerold L. MOSHER, Kansas City, MO;
 David W. MILES, Kansas City, MO;

Applicant(s)

Silvergate Pharmaceuticals, Inc., Greenwood Village, CO;

Power of Attorney: The patent practitioners associated with Customer Number 21971

Domestic Priority data as claimed by applicant

This application is a CON of 16/883,553 05/26/2020
 which is a CON of 16/242,898 01/08/2019
 which is a CON of 16/177,159 10/31/2018
 which is a CON of 16/003,994 06/08/2018 PAT 10154987
 which is a CON of 15/802,341 11/02/2017 PAT 10039745
 which is a CON of 15/613,622 06/05/2017 PAT 9808442
 which is a CON of 15/081,603 03/25/2016 PAT 9669008
 which claims benefit of 62/310,198 03/18/2016

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

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Projected Publication Date: 11/26/2020

Non-Publication Request: No

Early Publication Request: No

Title

ENALAPRIL FORMULATIONS

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/991,575	08/12/2020	Gerold L. MOSHER	43060-707.307	7887
<div> <div>21971</div> <div>7590</div> <div>08/25/2020</div> <div>WILSON, SONSINI, GOODRICH & ROSATI</div> <div>650 PAGE MILL ROAD</div> <div>PALO ALTO, CA 94304-1050</div> </div>			EXAMINER	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			08/25/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):
 patentdocket@wsgr.com

<i>Decision Granting Request for Prioritized Examination (Track I)</i>	Application No. 16/991,575	Applicant(s) MOSHER et al.	
	Examiner CHERYL P GIBSON BAYLOR	Art Unit OPET	AIA (FITF) Status Yes
<p>1. THE REQUEST FILED <u>12 August 2020</u> IS GRANTED .</p> <p>The above-identified application has met the requirements for prioritized examination</p> <p>A. <input checked="" type="checkbox"/> for an original nonprovisional application (Track I).</p> <p>B. <input type="checkbox"/> for an application undergoing continued examination (RCE).</p> <p>2. The above-identified application will undergo prioritized examination. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:</p> <p>A. filing a <u>petition for extension of time</u> to extend the time period for filing a reply;</p> <p>B. filing an <u>amendment to amend the application to contain more than four independent claims, more than thirty total claims</u>, or a multiple dependent claim;</p> <p>C. filing a <u>request for continued examination</u> ;</p> <p>D. filing a notice of appeal;</p> <p>E. filing a request for suspension of action;</p> <p>F. mailing of a notice of allowance;</p> <p>G. mailing of a final Office action;</p> <p>H. completion of examination as defined in 37 CFR 41.102; or</p> <p>I. abandonment of the application.</p> <p>Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.</p>			
/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET			

Doc Code: DIST.E.FILE**Document Description: Electronic Terminal Disclaimer - Filed**U.S. Patent and Trademark Office
Department of Commerce

Electronic Petition Request	TERMINAL DISCLAIMER TO OBIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	
Application Number	16991575	
Filing Date	12-Aug-2020	
First Named Inventor	Gerold MOSHER	
Attorney Docket Number	43060-707.307	
Title of Invention	ENALAPRIL FORMULATIONS	
<input checked="" type="checkbox"/> Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action <input checked="" type="checkbox"/> This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.		
Owner	Percent Interest	
Silvergate Pharmaceuticals, Inc.	100%	
The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s) 9669008 9808442 10039745 10154987 10786482 10772868 10799476		

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

☐ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicant claims the following fee status:

- ☐ Small Entity
- ☐ Micro Entity
- ☒ Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

☒ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 67024

☐ A sole inventor

☐ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

☐ A joint inventor; all of whom are signing this request

Signature	/Clark Lin/
Name	Clark Lin

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Doc Code: DISQ.E.FILE

Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16991575

Filing Date: 12-Aug-2020

Applicant/Patent under Reexamination: MOSHER

Electronic Terminal Disclaimer filed on December 16, 2020

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Attorney Docket No. 43060-707.304

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 3572
Serial No.: 16/177,159	Examiner: SPRINGER, Stephanie K
Filed: October 31, 2018	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on May 15, 2020, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u>/Paula Derby/</u></p>

Mail Stop Amendment

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132I, **Gerold Mosher**, state and declare as follows:

1. I am currently employed at Azurity Pharmaceuticals, Inc., a company formed in May 2019 by the acquisition of Silvergate Pharmaceuticals, Inc. by CutisPharma, Inc.

2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.

3. I have been employed at Silvergate Pharmaceuticals and now Azurity Pharmaceuticals since 2013, and my current position is Vice President of Product Development. As part of my job duties, I develop oral formulations for pediatric use. I have a small laboratory where I

develop, characterize and move formulations through the steps required for FDA approval and eventual sale.

4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also been employed by small startup companies to develop new solubilizing technology for oral, injectable, and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for about 40 years, and have extensive experience in developing pharmaceutical formulations. My *Curriculum Vitae* is attached as Exhibit A.

6. I am familiar with the subject matter claimed in U.S. Pat. App. Ser. No. 16/177,159 (“the ’159 application”), and I am a named inventor on this application. Silvergate Pharmaceuticals, Inc. is the assignee of all rights in the invention of the pending ’159 application.

7. I am aware of the Non-Final Office Action mailed in this matter on January 7, 2020. I am also aware that the pending claims were rejected under 35 U.S.C. 112(b) and 35 U.S.C. 112(a).

8. I am submitting this declaration to address some of the comments made in the Office Action,.

9. The ’159 application relates to enalapril oral liquid formulations that are stable at about 5 ± 3 °C for at least 12 months. The development of this described enalapril formulation was oriented on preparing a safe, stable, uniform oral liquid with minimal degradation and having an acceptable taste for pediatric patients.

10. Traditionally, approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in “Nahata” and subsequently administering the suspension to the patient, or (3) reconstituting a powder in a liquid carrier. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty swallowing solid oral dosage forms. For the second method,

extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination.

11. Compared to these currently available methods, the enalapril oral liquid formulation claimed in the '159 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

12. The oral enalapril liquid formulations of the '159 application have superior stability—they are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

13. The '159 application describes that stable oral enalapril liquid formulations can be prepared with suitable buffers including citrate buffers at varying concentrations. Formulations containing a mixture of citric acid and sodium citrate at various amounts as buffers are exemplified in the '159 application, for example, formulations B1-B3 in Example B and formulations E1-E6 in Example E. The buffer concentrations of formulations E1 to E6 are the following:

Buffer Concentration	E1	E2	E3	E4	E5	E6
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Citric acid (mg/mL)	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate (mg/mL)	0.75	0.75	0.75	0.75	0.38	0.19
Citrate concentration (mM)	20	20	20	20	10	5

14. The storage stability of formulations E1-E6 is summarized in Table E-2, partially copied below for the stability results at 5 °C. After storing at about 5 °C for a period of 52 or 62 weeks, the combined amount of two primary degradants, Enalaprilat and diketopiperazine, remained less than 1 % w/w, demonstrating excellent formulation stability. As shown in Table E-2, the formulations prepared with 5 mM, 10 mM or 20 mM of a mixture of citric acid and sodium citrate as a buffer have comparable stability over 52 weeks at about 5 °C.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)								
	Storage		Formulation					
	°C	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		

15. Further evidence of the superior stability of the citrate buffer-based formulations disclosed in the '159 application can be found in exemplary formulations H1 and H7-H13 presented below in Table 1, which all contain a mixture of citric acid and sodium citrate.

16. Formulations H1 and H7-H13 were prepared according to the compositions in Table 1 and titrated if needed to the target pH with 5N hydrochloric acid or 5N sodium hydroxide. Formulations H1 and H7-H9 were placed into HDPE containers and sealed with screw caps and induction sealing and stored at 5 °C. Formulations H10-H13 were placed into glass containers, sealed with Teflon lined screw caps and stored at 60 °C. The formulations were sampled at various

times during storage. Samples were analyzed by HPLC for enalapril maleate and enalapril related substances. The results of the analyses are presented in Table 2 and Table 3.

17. The enalapril maleate assay results in Table 2 show that formulations H1 and H7-H9 retain greater than 98% of the initial enalapril maleate content and have less than 2% of total impurity after 52 weeks at 5 °C. Formulations H1 and H7-H9 demonstrated excellent stability. Further, by comparing the amounts of the two primary degradants (i.e., Diketopiperazine and Enalaprilat) in Table 2 and Table E-2, it can be expected that formulations E1-E6 have comparable stability to formulations H1 and H7-H9.

18. In Table 3, the stability of formulations prepared with a mixture of citric acid and sodium citrate as a buffer at two different concentrations and pH values were compared under an accelerated condition at 60 °C. The results in Table 3 show that a citrate buffer concentration of about 10 mM or 20 mM, at least when adjusted to a pH value of about 3-4, are suitable to be used in formulations of the '159 application and yield similar stability.

Table 1

Compositions (mg/mL) for Stability Testing								
Ingredients	H1 Citrate	H7 Citrate	H8 Citrate	H9 Citrate	H10 Citrate	H11 Citrate	H12 Citrate	H13 Citrate
Citric acid, anhydrous	1.82	1.92	1.92	1.92	1.92	1.92	3.84	3.84
Sodium citrate, dihydrate	0.15	-	-	-				
Citrate concentration (mM)	10	10	10	10	10	10	20	20
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose NF	0.70	0.70	0.70	0.70				
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	qs	qs	qs	qs	qs	qs	qs	qs
pH	3.3	3.3	4.0	4.5	3	4	3	4

Table 2

Assay and Total Degradant Content After Storage						
	Storage		Formulation			
	°C	Weeks	H1	H7	H8	H9
Enalapril Maleate (% initial)	5	0	100.0	100.0	100.0	100.0
		2	100.1	100.7	100.4	100.3
		4	100.2	99.8	100.0	99.6
		8	100.0	99.6	100.9	100.7

		24	99.8	100.4	100.1	99.8
		28	99.8	99.7	-	-
		36	-	-	99.9	99.4
		52	99.9	99.8	99.5	99.2
Diketopiperazine (% w/w of enalapril maleate)	5	0	<0.05	<0.05	<0.05	<0.05
		2	<0.05	<0.05	<0.05	<0.05
		4	<0.05	<0.05	<0.05	<0.05
		8	<0.05	<0.05	<0.05	<0.05
		24	0.06	0.07	<0.05	<0.05
		28	0.09	0.10	-	-
		36	-	-	0.06	<0.05
		52	0.14	0.12	0.07	<0.05
Enalaprilat (% w/w of enalapril maleate)	5	0	<0.05	<0.05	0.09	0.10
		2	0.06	0.07	0.13	0.16
		4	0.08	0.08	0.17	0.24
		8	0.15	0.14	0.27	0.37
		24	0.19	0.20	0.41	0.58
		28	0.35	0.36	-	-
		36	-	-	0.85	1.17
		52	0.53	0.52	1.10	1.49
Total Impurities (% w/w of enalapril maleate)	5	0	<0.05	<0.05	0.09	0.10
		2	0.07	0.07	0.14	0.16
		4	0.09	0.10	0.20	0.26
		8	0.18	0.18	0.31	0.41
		24	0.25	0.27	0.43	0.60
		28	0.44	0.46	-	-
		36	-	-	0.91	1.20
		52	0.68	0.65	1.18	1.53

Table 3
Assay Results After Storage of Formulations at 60 °C

Buffer	mM	Enalapril Maleate, pH 3 (% initial)				Enalapril Maleate, pH 4 (% initial)			
		0 Days	2 Days	4 Days	7 Days	0 Days	2 Days	4 Days	7 Days
Citrate	10	100.0	97.1	97.2	95.5	100.0	97.2	96.6	94.6
	20	100.0	97.1	96.8	95.2	100.0	96.8	96.4	94.4

19. As presented above, Table E-2 and Tables 1-3 show that formulations of the '159 application can be prepared using a mixture of citric acid and sodium citrate, and the amount of the total citrate can vary, at least between about 5 mM and about 20 mM. All the formulations in Table E-2 and Tables 1-3 demonstrated superior stability, e.g., retaining greater than about 98% of the

initial enalapril maleate content and having less than about 2% w/w total impurity after 52 weeks at 5 °C.

20. Further, although formulations exemplified in the '159 application and in Tables 1-3 have a total citrate amount of about 5 mM, 10 mM or 20 mM, I would expect that similar formulations having a total citrate amount between about 5 mM and about 20 mM to have similar, superior stability as the exemplified formulations.

21. I declare that all statements made herein are true to the best of my knowledge, or if made upon information and belief, are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted on this 5th day of May, 2020

Gerold L. Mosher

Gerold L. Mosher, Ph.D.

Attorney Docket No. 43060-707.305

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Confirmation No.: 1032
Serial No.: 16/242,898	Examiner: SPRINGER, Stephanie K
Filed: January 8, 2019	Customer No.: 21971
Title: ENALAPRIL FORMULATIONS	<p align="center"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached Response and all accompanying papers is being deposited by Electronic Filing on May 14, 2020, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: <u>/Paula Derby/</u></p>

Mail Stop Amendment

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132I, **Gerold Mosher**, state and declare as follows:

1. I am currently employed at Azurity Pharmaceuticals, Inc., a company formed in May 2019 by the acquisition of Silvergate Pharmaceuticals, Inc. by CutisPharma, Inc.
2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.
3. I have been employed at Silvergate Pharmaceuticals and now Azurity Pharmaceuticals since 2013, and my current position is Vice President of Product Development. As part of my job duties, I develop oral formulations for pediatric use. I have a small laboratory where I

develop, characterize and move formulations through the steps required for FDA approval and eventual sale.

4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also been employed by small startup companies to develop new solubilizing technology for oral, injectable, and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for about 40 years, and have extensive experience in developing pharmaceutical formulations. My *Curriculum Vitae* is attached as Exhibit A.

6. I am familiar with the subject matter claimed in U.S. Pat. App. Ser. No. 16/242,898 (“the ’898 application”), and I am a named inventor on this application. Silvergate Pharmaceuticals, Inc. is the assignee of all rights in the invention of the pending ’898 application.

7. I am aware of the Final Office Action mailed in this matter on November 19, 2019. I am also aware that the pending claims stand rejected as allegedly being obvious under 35 U.S.C. 103 over Nahata et al., “Stability of enalapril maleate in three extemporaneously prepared oral liquids,” Am. J. Health-Syst. Pharm., 1998, vol. 55, pages 1155-1157 (“Nahata”) in view of Sosnowska et al., “Stability of Extemporaneous Enalapril Maleate Suspensions for Pediatric Use Prepared From Commercially Available Tablets,” Acta Poloniae Pharmaceutica - Drug Research, 2009, vol. 66, no. 3, pages 321-326 (“Sosnowska”) in view of Boukarim et al., “Preservatives in Liquid Pharmaceutical Preparations”, J. Appl. Res., 2009, vol. 9, no. 1&2, pages 14-17 (“Boukarim”). I have reviewed these cited references in the Final Office Action.

8. I am submitting this declaration to address the comments made in the Office Action.

9. The ’898 application relates to enalapril oral liquid formulations that are stable at about 5 ± 3 °C for at least 12 months. The development of this described enalapril formulation was oriented on preparing a safe, stable, uniform oral liquid with minimal degradation and having an acceptable taste for pediatric patients.

10. Traditionally, approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in “Nahata” and subsequently administering the suspension to the patient, or (3) reconstituting a powder in a liquid carrier. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty swallowing solid oral dosage forms. For the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination.

11. As compared to these currently available methods, the enalapril oral liquid formulation claimed in the '898 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

12. The oral enalapril liquid formulations of the '898 application have superior stability—they are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

13. Evidence of the superior stability of the formulations disclosed in the '898 application can be found in exemplary formulations H1 to H9. Formulations H1 to H9 were prepared according to the compositions in Table 1 and titrated if needed to the target pH with 5N hydrochloric acid or 5N sodium hydroxide. The formulations were placed into HDPE containers and sealed with screw caps and induction sealing. The formulations were stored at 5 °C and 25 °C and sampled at various times. Samples were analyzed by HPLC for enalapril maleate and enalapril related substances. The results of the analyses are presented in Table 2.

14. As shown in Table 1 below, formulations H1- H9 were prepared with a variety of buffers, including sodium citrate, citric acid, phosphate, citrate/phosphate, acetate, glycine, and tartrate. Formulations H1 and H7-H9 contain citrate-based buffers. Specifically, formulation H1 was prepared with citric acid and sodium citrate, and formulations H7-H9 were prepared with citric acid only (no sodium citrate) with the pH being adjusted with HCl or NaOH. Formulations H2-H6 were prepared with phosphate, citrate/phosphate, acetate, glycine, and tartrate buffer, respectively. The pH values of formulations H1 to H9 vary from about 3.3 to about 4.5. The initial pH values of formulations H1 to H7 are about 3.3, and the initial pH values of formulations H8 and H9 are about 4.0 and 4.5, respectively.

15. The enalapril maleate assay results in Table 2 show that all the formulations have greater than 98% of the initial enalapril maleate content remaining after 52 weeks at 5 °C. The total impurity content is also less than 2% for the same period showing comparable stability between the formulations, irrespective of the type of buffers used.

Table 1

Compositions (mg/mL) for Stability Testing at 5 °C and 25 °C									
	H1	H2	H3	H4	H5	H6	H7	H8	H9
Ingredients	Citrate	Phosphate	Citrate/ Phosphate	Acetate	Glycine	Tartrate	Citrate	Citrate	Citrate
Acetic acid, glacial	-	-	-	0.58	-	-	-	-	-
Sodium Acetate	-	-	-	0.04	-	-	-	-	-
Citric acid, anhydrous	1.82	-	1.07	-	-	-	1.92	1.92	1.92
Sodium citrate, dihydrate	0.15	-	-	-	-	-	-	-	-
Glycine	-	-	-	-	0.75	-	-	-	-
Sodium dihydrogen phosphate, anhydrous	-	1.2	-	-	-	-	-	-	-
Disodium hydrogen	-	-	0.63	-	-	-	-	-	-

phosphate, anhydrous

L-(+)-tartaric acid	-	-	-	-	-	0.75	-	-	-
Sodium tartrate dibasic, dihydrate	-	-	-	-	-	1.15	-	-	-
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose NF	0.70	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
pH	3.3	3.3	3.3	3.3	3.3	3.3	3.3	4.0	4.5

Table 2

Assay and Total Degradant Content After Storage											
	Storage		Formulation								
	°C	Weeks	H1	H2	H3	H4	H5	H6	H7	H8	H9
Enalapril Maleate (% initial)	5	0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
		2	100.1	100.1	99.7	100.0	99.5	98.2	100.7	100.4	100.3
		4	100.2	100.3	99.6	100.4	100.0	98.9	99.8	100.0	99.6
		8	100.0	100.0	99.7	100.0	99.5	98.5	99.6	100.9	100.7
		24	99.8	100.0	99.6	100.2	99.4	98.6	100.4	100.1	99.8
		28	99.8	99.9	99.6	100.1	99.3	98.4	99.7	-	-
		36	-	-	-	-	-	-	-	99.9	99.4
		52	99.9	99.9	99.7	99.7	98.9	98.1	99.8	99.5	99.2
	25	0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
		2	100.1	99.2	99.7	100.0	99.5	98.4	99.8	99.9	99.5
		4	99.7	99.1	99.4	99.9	99.4	98.5	99.1	99.0	98.1
		8	98.8	98.0	98.5	99.0	98.3	97.4	98.3	99.3	97.7
		24	98.0	97.2	97.7	98.4	98.1	96.9	98.4	97.5	95.3
		28	95.8	95.1	95.5	96.5	96.1	94.7	95.6	-	-
		36	-	-	-	-	-	-	-	93.7	89.4
		52	93.9	93.3	93.5	94.3	93.9	92.4	93.6	91.7	86.0
Total Impurities (% w/w of enalapril maleate)	5	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.09	0.10
		2	0.07	0.07	0.07	0.06	0.06	0.06	0.07	0.14	0.16
		4	0.09	0.11	0.10	0.11	0.11	0.12	0.10	0.20	0.26
		8	0.18	0.20	0.18	0.16	0.16	0.18	0.18	0.31	0.41
		24	0.25	0.29	0.26	0.24	0.22	0.25	0.27	0.43	0.60
		28	0.44	0.47	0.47	0.42	0.41	0.44	0.46	-	-
		36	-	-	-	-	-	-	-	0.91	1.20
		52	0.68	0.71	0.71	0.64	0.66	0.68	0.65	1.18	1.53
	25	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.09	0.10
		2	0.46	0.47	0.47	0.39	0.39	0.41	0.51	0.63	0.95
		4	0.86	0.91	0.89	0.83	0.81	0.88	0.89	1.16	1.84
		8	1.71	1.79	1.76	1.53	1.51	1.64	1.70	2.21	3.49
		24	2.52	2.65	2.60	2.24	2.21	2.40	2.49	3.28	5.27
		28	4.91	5.18	5.08	4.49	4.43	4.81	4.94	-	-

36	-	-	-	-	-	-	-	7.32	11.60
52	7.22	7.64	7.45	6.67	6.60	7.16	7.25	9.55	14.95

16. Further evidence of the superior stability of the formulations disclosed in the '898 application can be found in exemplary formulations in Table 3. Formulations in Table 3 were prepared using fumarate, tartrate, malate, aspartate, glycinate, lactate, formate, phthalate, acetate, succinate, gluconate, glutamate, citrate, phosphate, and citrate/phosphate buffers, respectively. Specifically, these formulations were prepared according to the compositions in Table 3 and titrated if needed to pH 3 and 4 with 5N hydrochloric acid or 5N sodium hydroxide. The formulations were placed into amber glass screw-capped vial with Teflon lined caps. The vials were capped, stored at 60 °C and sampled at various times over 7 days. Samples were analyzed by HPLC for enalapril. The results of the analyses are presented in Table 4.

17. The citrate and phosphate 10mM formulations were included in Table 3 as a control since citrate and phosphate buffers were included in the previous study in Tables 1 and 2 and demonstrated superior stability. The enalapril maleate assay results in Table 4 show that all the formulations have stability comparable to the citrate formulations at 60 °C.

Table 3

Compositions (mg/mL) for Stability Testing at 60 °C												
Formula	Fumarate		Tartrate		Malate		Aspartate		Glycinate		Lactate	
	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM
Fumaric acid	2.32	1.16	-	-	-	-	-	-	-	-	-	-
Tartaric acid	-	-	3.00	1.50	-	-	-	-	-	-	-	-
DL-Malic acid	-	-	-	-	2.68	1.34	-	-	-	-	-	-
L-Aspartic acid	-	-	-	-	-	-	2.66	1.33	-	-	-	-
Glycine	-	-	-	-	-	-	-	-	1.50	0.75	-	-
Lactic acid	-	-	-	-	-	-	-	-	-	-	180	90
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
5N HCl/5N NaOH to pH	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0
Formula	Formate		Phthalate		Acetate		Succinate		Gluconate		Glutamate	
	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM	20mM	10mM
Formic acid	0.92	0.46	-	-	-	-	-	-	-	-	-	-

Potassium hydrogen phthalate	-	-	4.08	2.04	-	-	-	-	-	-	-	-
Acetic acid, glacial	-	-	-	-	1.20	0.60	-	-	-	-	-	-
Succinic acid	-	-	-	-	-	-	2.36	1.18	-	-	-	-
Sodium gluconate	-	-	-	-	-	-	-	-	4.36	2.18	-	-
L-Glutamic acid	-	-	-	-	-	-	-	-	-	-	2.94	1.47
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
5N HCl/5N NaOH to pH	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0

Formula	Citrate		Phosphate		Citrate/Phosphate	
	20mM	10mM	20mM	10mM	10mM each	
Citric acid, anhydrous	3.84	1.92	-	-	1.92	
Phosphoric acid	-	-	196	98	98	
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	
Enalapril Maleate	1.00	1.00	1.00	1.00	1.00	
Purified water	Qs	Qs	Qs	Qs	Qs	
5N HCl/5N NaOH to pH	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	

TABLE 4

Assay Results After Storage of Formulations at 60 °C

Buffer	mM	Enalapril Maleate, pH 3 (% initial)				Enalapril Maleate, pH 4 (% initial)			
		0 Days	2 Days	4 Days	7 Days	0 Days	2 Days	4 Days	7 Days
Citrate	10	100.0	97.1	97.2	95.5	100.0	97.2	96.6	94.6
	20	100.0	97.1	96.8	95.2	100.0	96.8	96.4	94.4
Phosphate	10	100.0	97.1	97.1	95.3	100.0	96.3	96.2	94.5
	20	100.0	97.1	96.7	95.2	100.0	96.3	96.0	94.2
Citrate/Phosphate	20	100.0	96.8	97.3	95.2	100.0	96.8	96.2	94.9
Tartrate	10	100.0	97.4	97.6	95.9	100.0	96.9	97.0	95.2
	20	100.0	97.2	97.6	95.6	100.0	97.1	96.4	94.0
Glycinate	10	100.0	98.7	96.4	95.4	100.0	96.8	96.6	95.3
	20	100.0	98.3	96.9	95.7	100.0	96.7	97.3	96.0
Acetate	10	100.0	97.5	97.4	95.1	100.0	96.7	96.8	95.3
	20	100.0	97.4	98.2	95.2	100.0	97.1	96.8	94.9
Malate	10	100.0	97.2	97.1	96.0	100.0	97.0	96.8	95.2
	20	100.0	97.2	97.1	95.9	100.0	96.7	96.5	95.0
Fumarate	10	100.0	96.6	96.8	95.2	100.0	95.9	96.1	94.4
	20	100.0	96.6	96.6	94.7	100.0	95.8	95.8	93.6
Succinate	10	100.0	98.1	96.2	95.3	100.0	96.6	96.8	94.5

	20	100.0	96.9	97.3	95.1	100.0	96.2	96.9	94.6
Aspartate	10	100.0	97.3	97.1	96.1	100.0	96.5	98.1	96.4
	20	100.0	97.0	97.4	95.8	100.0	96.6	97.0	95.3
Formate	10	100.0	97.0	97.1	95.6	100.0	96.6	97.1	93.8
	20	100.0	96.9	96.5	96.3	100.0	96.1	98.1	93.3
Gluconate	10	100.0	97.2	97.9	95.2	100.0	96.3	96.2	93.4
	20	100.0	97.0	98.9	94.2	100.0	96.2	95.8	94.2
Glutamate	10	100.0	97.2	96.9	95.9	100.0	96.9	96.4	95.3
	20	100.0	97.3	97.1	95.2	100.0	96.7	97.5	93.7
Lactate	10	100.0	97.3	97.1	96.4	100.0	96.5	98.3	95.3
	20	100.0	97.3	97.2	97.2	100.0	96.9	96.3	95.2
Phthalate	10	100.0	97.3	96.9	95.8	100.0	96.2	96.2	94.7
	20	100.0	97.0	96.8	95.5	100.0	96.2	97.8	93.3

18. As presented above, Tables 1-4 show that the formulations of the '898 application can be prepared using a variety of buffers (e.g., citrate, phosphate, citrate/phosphate, acetate, glycinate, fumarate, tartrate, malate, aspartate, lactate, formate, phthalate, acetate, succinate, gluconate, and glutamate buffers) and the pH values of the formulations can vary, e.g., at least from about 3 to about 4.5. All the formulations in Tables 1 and 3 demonstrated superior stability—retaining greater than 98% of the initial enalapril maleate content and having less than 2% w/w total impurity after 52 weeks at 5 °C, or having comparable stability when tested under an accelerated condition of 60 °C.

19. In my review of the references cited in the Office Action, none of the references describe this stability of at least 12 months at 5±3 °C or any means of achieving this stability for enalapril formulations.

20. I have reviewed Nahata which describes the extemporaneous preparation of oral liquid enalapril formulations by crushing enalapril tablets with a mortar and pestle and suspending the resulting ground tablets in water, citrate buffer, or Ora-Plus/Ora-Sweet. On stability, Nahata states that the “compounded oral liquids [were] stable for 91 days at 4 and 25 °C” defining stable as “concentration after storage was ≥90% of the initial concentration. Table 1 of Nahata shows that the enalapril extemporaneous formulations exhibited about 5% loss of enalapril after about 56 days at 4 °C and about 5% loss of enalapril after about 91 days at 25 °C.

21. I have reviewed Sosnowska, which similarly describes extemporaneous enalapril suspensions. The suspensions disclosed in Sosnowska were obtained by grinding tablets and suspending the resultant powder in a hydroxyethylcellulose solution or in a mixture that contains raspberry syrup and hydroxyethylcellulose solution. Based on the 30-day stability data shown in Table 1 of Sosnowska, these extemporaneous formulations have comparable stabilities to the formulations of Nahata, which is retaining about 98% of initial enalapril concentration after stored at refrigerated condition for 30 days. As noted in Sosnowska, “in the absence of microbiological data, the shelf-life given to extemporaneous products containing preservatives is usually 30 days.” Page 325 of Sosnowska.

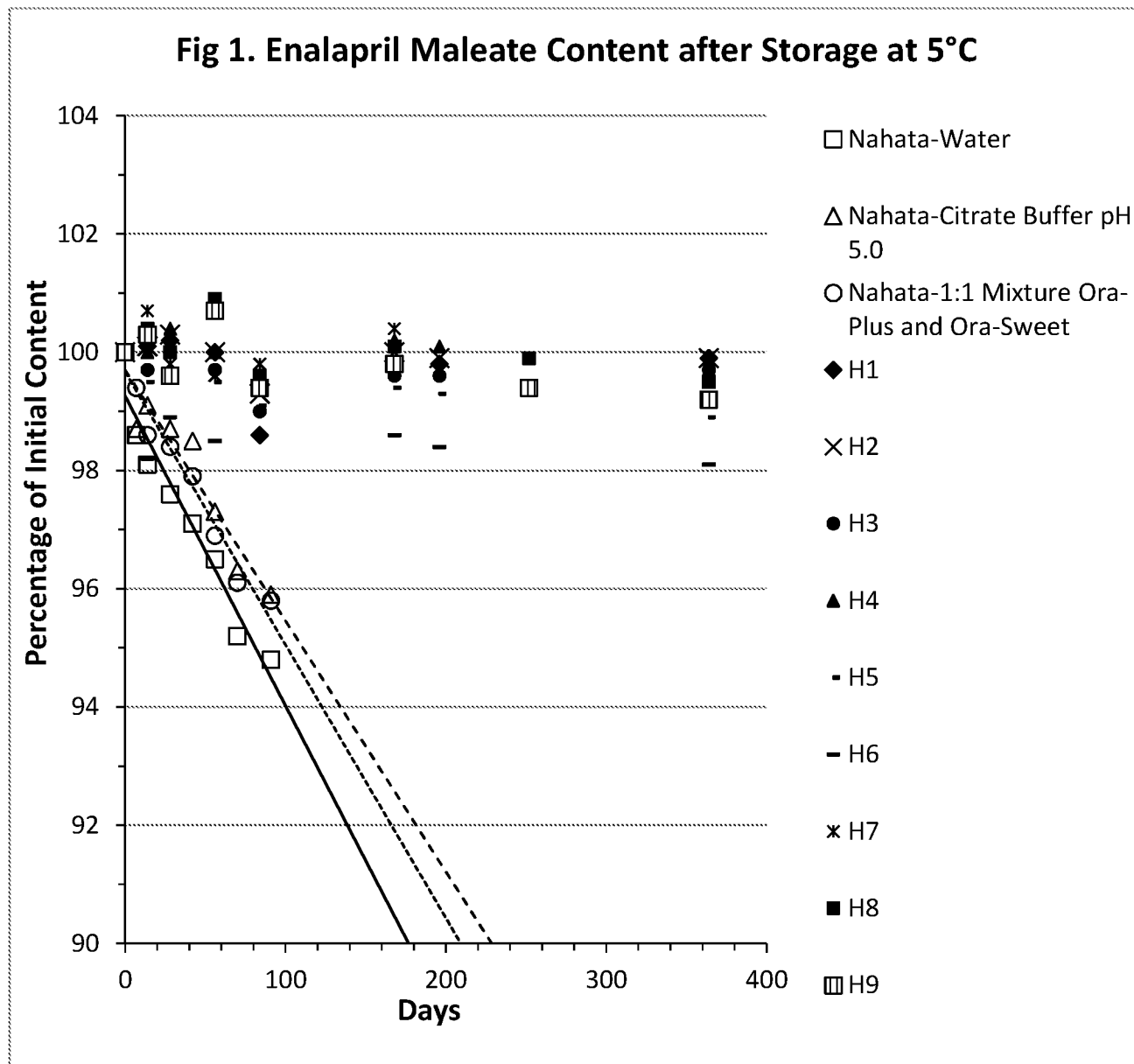
22. I have also reviewed Boukarim, which does not provide the stabilities of liquid enalapril formulations.

23. To compare the stability of the enalapril oral liquid formulations of the instant application with the extemporaneous preparations, such as those described in Nahata, the enalapril content of the Nahata formulations and that of formulations H1-H9 (stored at 5 °C) are provided in Table 5.

Table 5: Enalapril content in formulations after storage at 5 °C

Days	Nahata			Formulations of Instant Application								
	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	H1	H2	H3	H4	H5	H6	H7	H8	H9
0	100	100	100	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
7	98.6	98.7	99.4									
14	98.1	99.1	98.6	100.1	100.1	99.7	100.0	99.5	98.2	100.7	100.4	100.3
28	97.6	98.7	98.4	100.2	100.3	99.6	100.4	100.0	98.9	99.8	100.0	99.6
42	97.1	98.5	97.9									
56	96.5	97.3	96.9	100.0	100.0	99.7	100.0	99.5	98.5	99.6	100.9	100.7
70	95.2	96.3	96.1									
84				98.6	99.3	99.0	99.5	99.1	99.4	99.8	99.6	99.4
91	94.8	95.9	95.8									
168				99.8	100.0	99.6	100.2	99.4	98.6	100.4	100.1	99.8
196				99.8	99.9	99.6	100.1	99.3	98.4	99.7		
252											99.9	99.4
364				99.9	99.9	99.7	99.7	98.9	98.1	99.8	99.5	99.2

24. To further describe the contrast in stability, the enalapril concentrations published by Nahata, and the concentrations from H1-H9 are plotted graphically in Figure 1 with linear regression of the data for extrapolation.



25. Table 5 and Figure 1 show that formulations H1 to H9 exhibit excellent stability for at least 12 months (52 weeks) at 5 °C with essentially no or little loss of enalapril content, in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at about 5 °C for more

than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.

26. The enalapril content and total impurity data submitted in Tables 1-5 and Figure 1 show that the formulations of the present application are significantly more stable than the extemporaneously prepared formulations. Further, as shown by the stability of formulations H1-H9 and formulations of Table 3, a variety of buffers, which are capable of maintaining the pH values of the formulations at about or below 4.5, can be used in the formulations of the present application.

27. I declare that all statements made herein are true to the best of my knowledge, or if made upon information and belief, are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted on this 14th day of May, 2020



Gerold L. Mosher, Ph.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Art Unit: 1629
Inventors: Gerold L. Mosher, <i>et al.</i>	Examiner: Stephanie K. Springer
Serial No.: 15/081,603	Confirmation No.: 3892
Filed: March 25, 2016	Customer No.: 021971
Title: ENALAPRIL FORMULATIONS	

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEROLD MOSHER UNDER 37 C.F.R. § 1.132

I, **Gerold Mosher**, do hereby declare as follows:

1. I am currently employed at Silvergate Pharmaceuticals, Inc.
2. I received my Bachelor's degree in Pharmacy from the University of Kansas in 1979. I also received a Master and a Doctor of Philosophy in Pharmaceutical Chemistry in 1984 and 1986, respectively, from the University of Kansas.
3. I have been employed at Silvergate Pharmaceuticals since 2013, as Vice President of Drug Development. As part of my job duties, I develop oral solutions for pediatric use. I have a small laboratory where I develop, characterize and move formulations through the steps required for FDA approval and eventual sale.
4. Early in my career, I practiced pharmacy for two years from 1979 to 1981. Subsequently, I worked in large pharmaceutical companies (Eli Lilly and Merck) for about ten years where I focused primarily on pre-formulation and early phase formulations of new drug products. After leaving these companies and prior to Silvergate Pharmaceuticals, I have also

been employed by small startup companies to develop new solubilizing technology for oral, injectable and inhalation formulations.

5. In total, I have been in the field of pharmaceutical chemistry for almost 38 years, and have extensive experience in developing pharmaceutical formulations. My Curriculum Vitae is attached as Exhibit A.

6. I am familiar with the subject matter claimed in patent application 15/081,603, and am a named inventor on this application. Silvergate Pharmaceuticals is also the Assignee of the '603 application.

7. I am aware of the Non-Final Office Action mailed in this matter on January 17, 2017. I am also aware that the oral enalapril liquid formulation claims stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over US 8,568,747, Nahata et al. (Stability of Enalapril Maleate in three Extemporaneously Prepared Oral Liquids) ("Nahata"), Product Information of Bicitra (Sodium Citrate and Citric Acid Oral Solution) ("Bicitra"), Product Information of Ora-Sweet ("Ora-sweet"), and Rippley et al. (Pharmacokinetics Assessment of an Oral Enalapril Suspension for Use in Children) ("Rippley"). I have reviewed these cited references in the Non-Final Office Action.

8. I am submitting this declaration to address the comments made in the Office Action.

9. The '603 application relates to enalapril oral liquid formulations that are stable for least 12 months at 5 ± 3 °C. The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water at a pH of less than 3.5. Development of this described enalapril formulation was oriented on preparing a safe, stable, soluble oral liquid with minimal degradation and having acceptable taste for pediatric patients.

10. The currently approved methods of delivering enalapril to pediatric patients requires (1) administering a solid enalapril tablet or portion thereof to the patient, (2) extemporaneously preparing an oral liquid suspension from enalapril tablets and a diluent, such as the method described in "Nahata" and subsequently administering the suspension to the

patient, or (3) reconstituting a powder in a liquid carrier, such as the described enalapril powder in US 8,568,747.

11. All of these methods are undesirable and have limitations. For tablets, it is well known that children have difficulty in swallowing oral dosage forms. For the second method, extemporaneously prepared oral liquids present additional challenges and issues with respect to dosing accuracy and stability, as well as can introduce compounding errors and cross-contamination. Similarly, reconstituting powders into a liquid carrier also requires an extra step and could introduce variability, solubility and contamination issues during the reconstitution.

12. As compared to these currently available methods, the enalapril oral liquid formulations claimed in the '603 application provides several advantages:

- Improved ease of administration. It is easier for many patients to swallow a liquid than to swallow a tablet,
- Patient Compliance. Patients are more likely to take a dose that is not difficult to swallow, or difficult to prepare,
- Accuracy of dosing. The prescribing information for enalapril tablets provides dosing guidelines based on the weight of the child. When one only has fixed 2.5, 5 or 10 mg tablets available, it is difficult if not impossible to break the tablets in such a way to get an exact dose if the dose is something other than the tablet strength. In addition, if tablets are compounded into a suspension, the tablets are crushed in a mortar and then mixed with a liquid. There is no guarantee that the drug dissolves in, or is dispersed evenly in the liquid (thus leading to potential dosing errors. Moreover, there is always the chance of contamination of the resulting liquid by residual drugs or substances in the mortar. Similarly, in reconstitutable powders, there is also no guarantee that the powder dissolves or disperses evenly in the diluent.

13. It should be appreciated that the oral enalapril liquid formulations of the present claims are stable at 5 ± 3 °C for 12 months or longer with minimal degradation. The stability is an important aspect of the present formulations. It contributes to the consistency and uniformity of the formulations as well as allows for accuracy of dosing to patients.

14. Evidence of this stability is found in exemplary formulations E7 and E8 which show minimal degradation as compared to current formulations. In this study, exemplary formulations E7 and E8 were stored at either refrigerated condition (5 °C) or at ambient condition (25 °C). Formulations details for E7 and E8 are as follows:

Composition of Enalapril Maleate Formulations		
Component	E7	E8
Enalapril maleate	1.00	1.00
Citric acid anhydrous	1.80	1.82
Sodium citrate anhydrous	0.16	0.15
Sodium benzoate	1.00	1.00
Sucralose	0.70	0.70
Mixed berry flavor	0.50	0.50
Water	qs	qs
pH (measured)	3.3	3.3

qs = sufficient quantity

15. In my review of the references cited in the Office Action, none of the references describe this stability of at least 12 months at 5±3 °C or any means of achieving this stability for enalapril formulations.

16. I have reviewed Nahata which describes the extemporaneous preparation of oral liquid enalapril formulations by crushing enalapril tablets with a mortar and pestle and suspending the resulting ground tablets in water, citrate buffer, or Ora-Plus/Ora-Sweet. On stability, Nahata states that the “compounded oral liquids [were] stable for 91 days at 4 and 25 °C” defining stable as “concentration after storage was ≥90% of the initial concentration. Table 1 of Nahata shows that the enalapril extemporaneous formulations exhibited about 5% loss of enalapril after about 56 days at 4 °C and about 5% loss of enalapril after about 91 days at 25 °C.

17. I have also reviewed US 8,568,747 which describes an oral liquid enalapril formulation obtained by reconstituting an enalapril powder in a liquid. The table in example 6 of US 8,568,747 shows that the resulting oral liquid formulation exhibited about 5% loss of enalapril after about 8 weeks at 25 °C.

18. I additionally reviewed Bicitra, Ora-sweet, and Rippley and they do not provide any stability of enalapril formulations whatsoever.

19. To compare the stability of the enalapril extemporaneous preparations as described in Nahata and the reconstituted liquid formulation of US 8,568,747, I submit the following data which depicts the enalapril content of formulations E7 at 5°C and 25 °C and E8 at 5 °C in Table A and Table B:

Table A: Enalapril content in formulations after storage at 5 °C¹

	Nahata				
Days	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	E7	E8
0	100	100	100	100	100
7	98.6	98.7	99.4		
14	98.1	99.1	98.6		
28	97.6	98.7	98.4		
40				100.9	
42	97.1	98.5	97.9		100.3
56	96.5	97.3	96.9		
70	95.2	96.3	96.1		
91	94.8	95.9	95.8		
99				104.7	
205				101.1	
290				101.0	
383				99.7	
581				99.1	

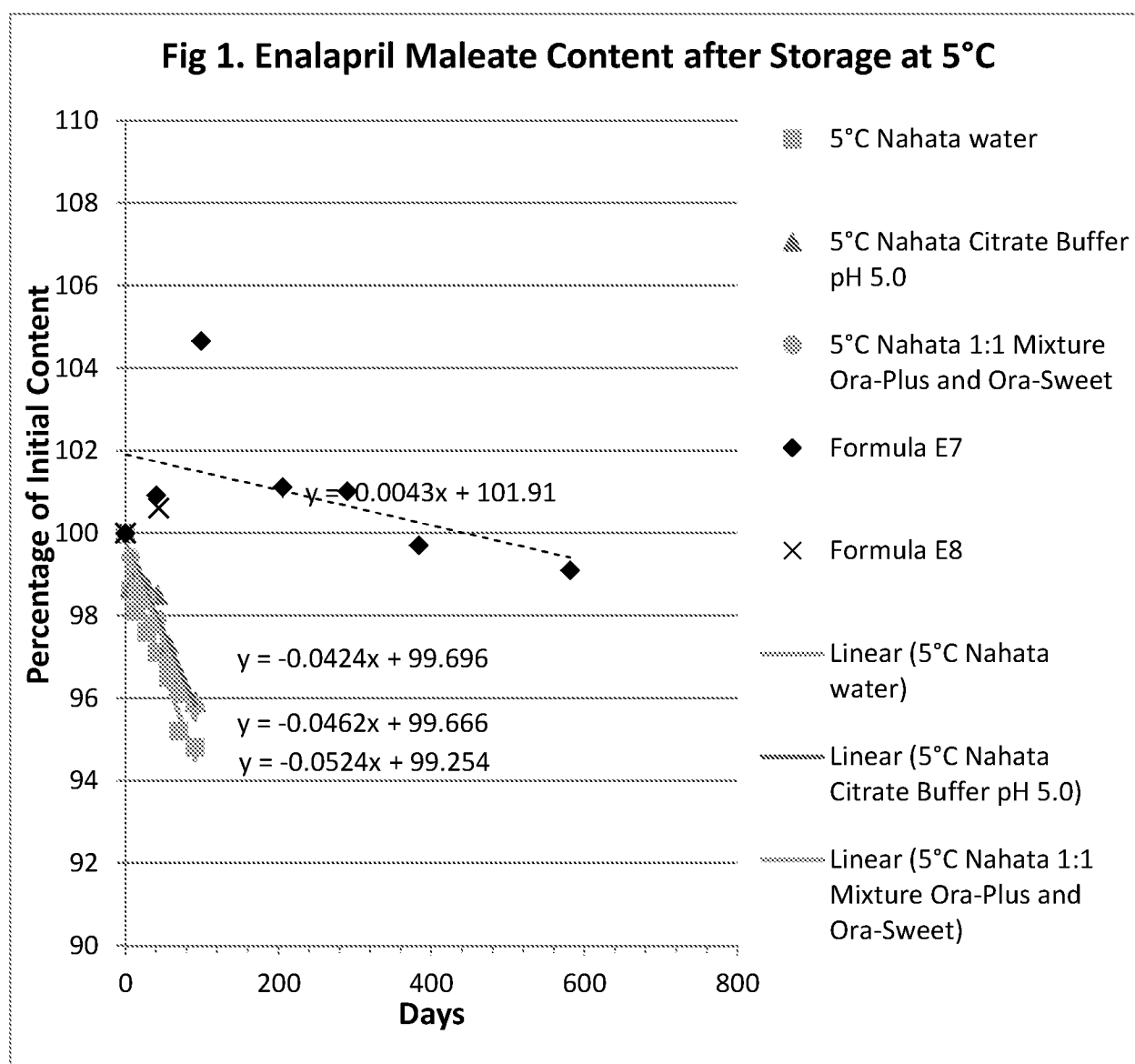
Table B: Enalapril content in formulations after storage at 25 °C

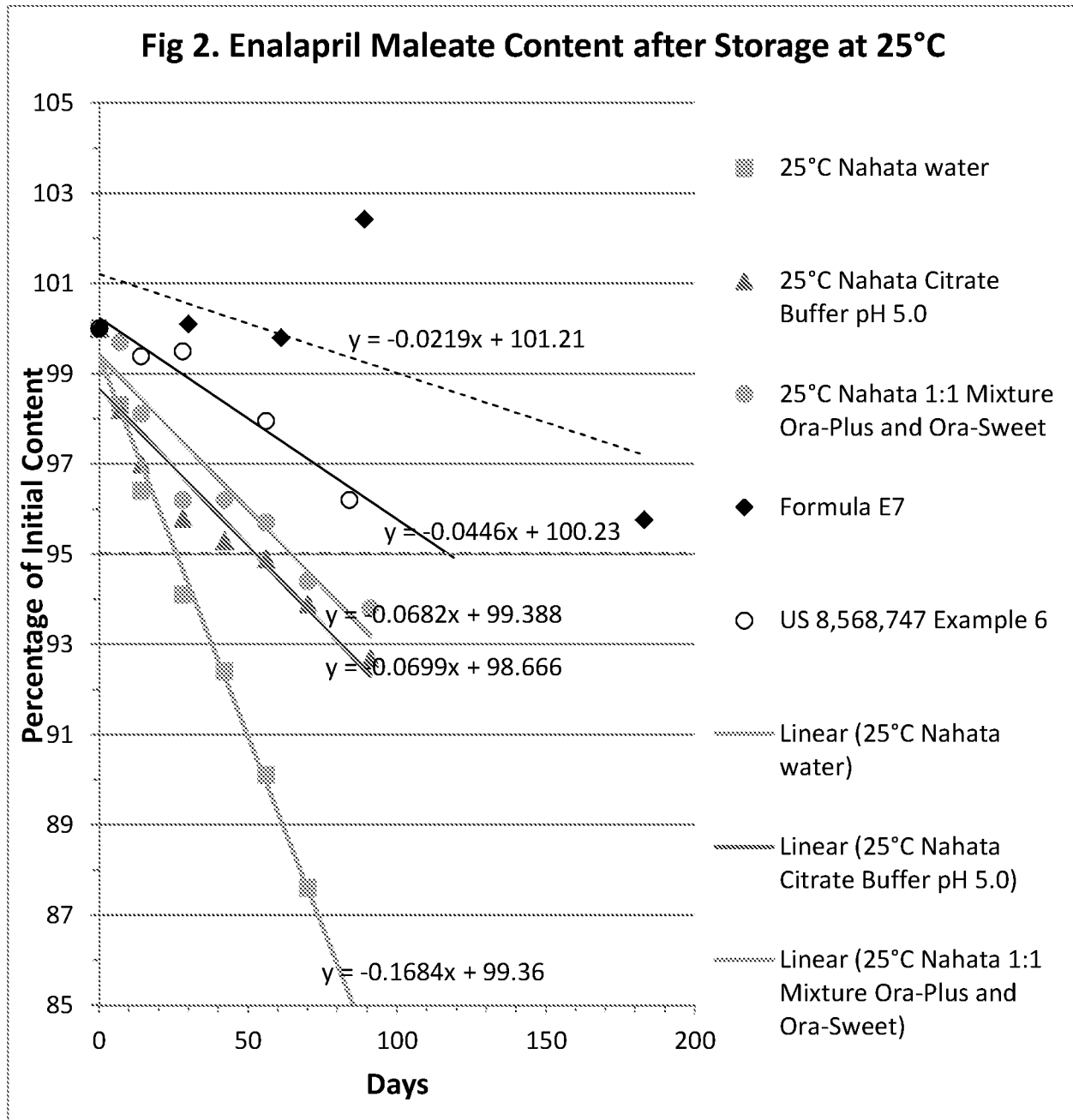
	Nahata			US 8,568,747	
Days	water	Citrate Buffer pH 5.0	1:1 Ora-Plus/Ora-Sweet	Example 6	E7
0	100	100	100	100	100
7	98.3	98.2	99.7		
14	96.4	97	98.1	99.4	
28	94.1	95.8	96.2	99.5	
30					100.1
42	92.4	95.3	96.2		
56	90.1	94.9	95.7	97.9	
61					99.8

¹ I note that US 8,568,747 does not provide stability data of the reconstituted liquid formulation at 5 °C.

70	87.6	93.9	94.4		
84				96.2	
89					102.4
91	84.1	92.7	93.8		
183					95.8

20. To further describe the contrast in stability, the enalapril concentrations published by Nahata, the US 8,568,747 enalapril concentrations, and the concentrations from E7 and E8 are plotted graphically (Fig. 1: 5 °C and Fig. 2: 25 °C) with linear regression of the data for extrapolation.





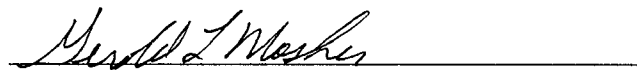
21. Table A and Fig. 1 show that E7 exhibits excellent stability for at least 18 months (581 days) at 5 °C with essentially no loss of enalapril content in contrast to the extemporaneous preparations of Nahata (stability is defined as no more than 5% formation of degradants and 5% loss of enalapril). While Nahata does not disclose stability at 5 °C for more than 90 days, the extrapolated lines show that at about 100 days, the extemporaneous preparations are unstable with respect to the enalapril content in the preparation.

22. Table B and Fig. 2 show that E7 also exhibits better stability for at least 6 months (183 days) at 25 °C in contrast to the Nahata preparations and the reconstituted formulation of US 8,568,747.

23. The additional enalapril content data submitted for E7 and E8 shows that the formulations of the present application are significantly more stable, which in my opinion reflects the superior results and advantages, obtained with the oral liquid enalapril formulation of the present claims.

24. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under 18 U.S.C. 1001.

Respectfully submitted on this 2nd day of February, 2017

A handwritten signature in cursive script, appearing to read "Gerold L. Mosher", is written over a horizontal line.

Gerold L. Mosher, Ph.D.

Electronically Filed: December 28, 2020

Attorney Docket No.: 43060-707.307

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)	Group Art Unit: 1629
)	
Inventor: Gerold L. Mosher, et al.)	Examiner: Savitha M. Rao
)	
Application No.: 16/991,575)	Confirmation No.: 7887
)	
Filed: August 12, 2020)	Customer No.: 021971
)	
For: ENALAPRIL FORMULATIONS)	
)	

SUPPLEMENTAL RESPONSE

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This communication is a supplemental response submitted in accordance with a communications between the Patent Office and the Applicant's representative on December 17, 2020 and December 28, 2020

Applicant respectfully requests allowance of the above-referenced application in view of the following response.

Summary of the Interview, Terminal Disclaimers, and Affidavits appear on page 2 of this paper.

Conclusion is on page 3 of this paper.

Application No.: 16/991,575
Atty. Docket No. 43060-707.307

SUMMARY OF THE INTERVIEW

Applicant is appreciative of Examiner Savitha M. Rao for extending the courtesy of an examiner's interview to Applicant's representatives, Clark Lin, on December 17, 2020 and the subsequent communication on December 28, 2020. A response consistent with those detailed herein was discussed.

TERMINAL DISCLAIMERS

As discussed in the interview, Applicant submitted terminal disclaimers on December 16, 2020, with respect to U.S. Patent No. 9,669,008, U.S. Patent No. 9,808,442, U.S. Patent No. 10,039,745, U.S. Patent No. 10,154,987, U.S. Patent No. 10,799,476, U.S. Patent No. 10,772,868, and U.S. Patent No. 10,786,482.

The terminal disclaimers have been approved.

AFFIDAVITS

As per the subsequent communication, Applicant hereby submits the following listed affidavits under 37 C.F.R. section 1.132. Also submitted is a recent CV of Dr. Gerold Mosher.

- Declaration of Gerold Mosher, dated May 14, 2020, filed for the application serial no. 16/242,898 on May 14, 2020
- Declaration of Gerold Mosher, dated February 2, 2017, filed for the application serial no. 16/242,898 on August 1, 2019
- Declaration of Gerold Mosher, dated May 15, 2020, filed for the application serial no. 16/177,159 on May 15, 2020
- Curriculum Vitae of Dr. Gerold Mosher

Application No.: 16/991,575
Atty. Docket No. 43060-707.307

CONCLUSION

Applicant believes that the Application is in condition for allowance and respectfully solicits the Examiner to expedite prosecution of this application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (617) 598-7823.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 43060-707.307).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Date: December 28, 2020

By: ____/Clark Lin/____
Clark Lin, Ph.D., J.D.
Reg. No. 67,024

650 Page Mill Road
Palo Alto, California 94304
Telephone No.: (650) 493-9300
Facsimile No.: (650) 493-6811
Customer No. 021971



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 01/01/2021
 WILSON SONSINI GOODRICH & ROSATI
 650 PAGE MILL ROAD
 PALO ALTO, CA 94304-1050

EXAMINER

RAO, SAVITHA M

ART UNIT

PAPER NUMBER

1629

DATE MAILED: 01/01/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/991,575	08/12/2020	Gerold L. MOSHER	43060-707.307	7887

TITLE OF INVENTION: ENALAPRIL FORMULATIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	04/01/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

21971 7590 01/01/2021
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/991,575	08/12/2020	Gerold L. MOSHER	43060-707.307	7887

TITLE OF INVENTION: ENALAPRIL FORMULATIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	04/01/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	514-001000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/991,575	08/12/2020	Gerold L. MOSHER	43060-707.307	7887
21971	7590	01/01/2021	EXAMINER	
WILSON SONSINI GOODRICH & ROSATI			RAO, SAVITHA M	
650 PAGE MILL ROAD			ART UNIT	
PALO ALTO, CA 94304-1050			PAPER NUMBER	
			1629	
DATE MAILED: 01/01/2021				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/991,575	Applicant(s) MOSHER et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 08/12/2020.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 1-30. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. <input type="checkbox"/> Notice of References Cited (PTO-892) 2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>11/30/2020</u> . 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. <input checked="" type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date. <u>12/17/2020</u> .	5. <input type="checkbox"/> Examiner's Amendment/Comment 6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance 7. <input type="checkbox"/> Other _____.
---	--

/SAVITHA M RAO/
Primary Examiner, Art Unit 1629

Application/Control Number: 16/991,575
Art Unit: 1629

Page 2

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-30 are pending in the instant application.

In the interest of compact prosecution, Examiner contacted the applicants requesting that they file an electronic terminal disclaimer to overcome the pending obviousness double patenting rejection over parent applications and also to refile the declaration by Gerold Mosher under 37 C.F.R 1.132 which details the stability data. Applicants agreed for both, see the attached interview summary with Mr. Clark Lin.

Information Disclosure Statement

The information disclosure statement (IDS) dated 11/30/2020 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Priority

This application is a continuation of US .Patent Application No 16/883553 filed 05/26/2020 (granted as US patent 10,799,476) which is a continuation of U.S. Patent Application No. 16/242,898, filed January 8, 2019 (granted as US patent 10,786,482) , which is a continuation of 16/177,159, filed October 31, 2018 (granted as US patent 10,772,868, which is a continuation of U.S. Patent Application No. 16/003,994, filed

Application/Control Number: 16/991,575

Page 3

Art Unit: 1629

June 8, 2018 (now U.S. Patent No. 10,154,987, issued December 18, 2018), which is a continuation of U.S. Patent Application No. 15/802,341, filed November 2, 2017 (now U.S. Patent No. 10,039,745, issued August 7, 2018), which is a continuation of U.S. Patent Application No. 15/613,622, filed June 5, 2017 (now U.S. Patent No. 9,808,442, issued November 7, 2017), which is a continuation of U.S. Patent Application No. 15/081,603, filed March 25, 2016 (now U.S. Patent No. 9,669,008, issued June 06, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed March 18, 2016

Terminal disclaimer

The terminal disclaimer filed on 12/16/2020 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **US patents 9669008, 9808442, 10039745, 10154987, 10772868, 10786482 and 10799476** have been reviewed and is accepted. The terminal disclaimer has been recorded.

Rule 37 CFR 1.132 Declaration

Applicant's submission of three sets of declarations of Gerold Mosher under 37 CFR 1.132 filed 12/28/2020 is acknowledged. The declarations is found to be persuasive in overcoming any art of record, as it clarifies the novelty of the instantly claimed composition.

REASONS FOR ALLOWANCE

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Art Unit: 1629

In view of the declarations, terminal disclaimers and the following statement of reasons for allowance, claims 1-30 are found to be allowable.

Following a diligent search it was determined that the prior art neither teaches nor suggests a stable oral liquid formulation, consisting essentially of (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM; (iii) a preservative, wherein the preservative is a paraben or a mixture of parabens; and (iv) water; wherein the formulation optionally comprises a sweetener, a flavoring agent, or both; wherein the formulation is stable at about 5 + 3 0C for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period. It is also noted that claimed formulation has been found to be novel and unobvious and has been allowed and issued in the Parent patents

Conclusion

Claims 1-30 are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

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Art Unit: 1629

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA M RAO/
Primary Examiner, Art Unit 1629

<i>Applicant-Initiated Interview Summary</i>	Application No. 16/991,575	Applicant(s) MOSHER et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	AIA (FITF) Status Yes

All participants (applicant, applicants representative, PTO personnel):

(1) SAVITHA M. RAO. (3) ____.

(2) Clark Lin. (4) ____.

Date of Interview: 17 December 2020.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: ____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1.

Identification of prior art discussed: none.

Substance of Interview

(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

In the interest of compact prosecution, Examiner contacted the applicants requesting that they file an electronic terminal disclaimer to overcome the pending obviousness double patenting rejection over parent applications and also to refile the declaration by Gerold Mosher under 37 C.F.R 1.132 which details the stability data. Applicants agreed for both,.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/SAVITHA M RAO/
Primary Examiner, Art Unit 1629

Summary of Record of Interview Requirements**Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record**

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews

Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

21971 7590 01/01/2021
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Pamela J. Pari	(Typed or printed name)
/Pamela J. Pari/	(Signature)
January 6, 2021	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/991,575	08/12/2020	Gerold L. MOSHER	43060-707.307	7887

TITLE OF INVENTION: ENALAPRIL FORMULATIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	04/01/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	514-001000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Wilson Sonsini Goodrich & Rosati, P.C.

2

3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

SILVERGATE PHARMACEUTICALS, INC.

Greenwood Village, Colorado

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 23-2415

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29☐ Applicant asserting small entity status. See 37 CFR 1.27☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Chen, Ying/

Date January 6, 2021

Typed or printed name Ying Chen

Registration No. 72,136



UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/991,575	02/16/2021	10918621	43060-707.307	7887

21971 7590 01/27/2021

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050**ISSUE NOTIFICATION**

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Gerold L. MOSHER, Kansas City, MO;
Silvergate Pharmaceuticals, Inc., Greenwood Village, CO;
David W. MILES, Kansas City, MO;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.